ISSN 2220-3141 (online)

World Journal of

Critical Care Medicine

World J Crit Care Med 2020 January 31; 9(1): 1-12

Published by Baishideng Publishing Group Inc

WJCCM

World Journal of Critical Care Medicine

Contents

Irregular Volume 9 Number 1 January 31, 2020

ORIGINAL ARTICLE

Observational Study

World Journal of Critical Care Medicine

Irregular Volume 9 Number 1 January 31, 2020

Contents

ABOUT COVER

AIMS AND SCOPE

The primary aim of the *World Journal of Critical Care Medicine* (*WJCCM*, *World J Crit Care Med*) is to provide scholars and readers from various fields of critical care medicine with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCCM mainly publishes articles reporting research results and findings obtained in the field of critical care medicine and covering a wide range of topics including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, ICU management and treatment control, sedation and analgesia, severe infection, *etc.*

INDEXING/ABSTRACTING

The *WJCCM* is now indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Irregular

EDITORS-IN-CHIEF
KLE Hon

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

PUBLICATION DATE
January 31, 2020

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2020 January 31; 9(1): 1-12

DOI: 10.5492/wjccm.v9.i1.1

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Observational Study

Experience with hemoadsorption (CytoSorb®) in the management of septic shock patients

Yatin Mehta, Chitra Mehta, Ashish Kumar, Joby Varghese George, Aditi Gupta, Saurabh Nanda, Gourav Kochhar, Arun Raizada

ORCID number: Yatin Mehta 0000-0003-2492-6687; Chitra Mehta 0000-0002-6738-1042; Ashish Kumar 0000-0001-9809-3513; Joby V George 0000-0002-7637-8929; Aditi Gupta 0000-0001-9713-4993; Saurabh Nanda 0000-0002-1462-4901; Gaurav Kochhar 0000-0001-6151-3684; Arun Raizada 0000-0002-3058-4014.

Author contributions: Mehta Y, Mehta C, Kumar A and Raizada A contributed to study conception and design; George JV, Gupta A, Nanda S, and Kochhar G contributed to data acquisition, data analysis and interpretation, and writing of article; Mehta Y, Mehta C, and Kumar A contributed to editing, reviewing and final approval of article.

Institutional review board statement: this study was reviewed and approved by an institutional ethics committee.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Yatin Mehta, Chitra Mehta, Ashish Kumar, Joby Varghese George, Aditi Gupta, Saurabh Nanda, Gourav Kochhar, Arun Raizada, Medanta The Medicity, Gurgaon 122001, Haryana, India

Corresponding author: Yatin Mehta, FRCA, MD, MNAMS, Doctor, FAMS, FIACIA, FICCM, FIEE, Chairman, Institute of Critical Care and Anesthesiology, Medanta the Medicity, Sector 38, Gurgaon 122006, Haryana, India. yatin.mehta@medanta.org

Abstract

BACKGROUND

Cytokines and inflammatory mediators are the hallmarks of sepsis. Extracorporeal cytokine hemoadsorption devices are the newer clinical support system to overcome the cytokine storm during sepsis.

AIM

To retrospectively evaluate the clinical outcomes of patients admitted in intensive care unit with septic shock with different etiologies.

METHODS

The laboratory parameters including biomarkers such as procalcitonin, serum lactate and C-reactive protein; and the hemodynamic parameters; mean arterial pressure, vasopressor doses, sepsis scores, cytokine levels and other vital parameters were evaluated. We evaluated these outcomes among survivors and non-survivors.

RESULTS

Of 100 patients evaluated, 40 patients survived. Post treatment, the vasopressors dosage remarkably decreased though it was not statistically different; 34.15% (P = 0.0816) for epinephrine, 20.5 % for norepinephrine (P = 0.3099) and 51% (P = 0.0678) for vasopressin. In the survivor group, a remarkable reduction of biomarkers levels; procalcitonin (65%, P = 0.5859), C-reactive protein (27%, P = 0.659), serum lactate (27%, P = 0.0159) and bilirubin (43.11%; P = 0.0565) were observed from baseline after CytoSorb® therapy. A significant reduction in inflammatory markers; interleukin 6 and interleukin 10; (87% and 92%, P < 0.0001) and in tumour necrosis factor (24%, P = 0.0003) was also seen. Overall, 28 (28%) patients who were given CytoSorb® therapy less than 48 h after onset of septic shock survived and the maximum duration of stay for 70% of these patients in

STROBE statement: Yes, we have read the Strobe statement and prepared checklist and the manuscript accordingly.

Manuscript source: Unsolicited Manuscript

Received: October 11, 2019
Peer-review started: October 11, 2019
First decision: November 1, 2019
Revised: December 23, 2019
Accepted: January 13, 2020
Article in press: January 13, 2020
Published online: January 31, 2020

P-Reviewer: Yeh YC, Spasojevic SD, Okumura K, Xavier-Elsas P
S-Editor: Wang YQ
L-Editor: A
P-Editor: Qi LL

intensive care unit was less than 15 d.

CONCLUSION
CytoSorb® is a safe and well tolerated rescue therapy option in patients with septic shock. However, early (preferably within < 48 h after onset of septic shock) initiation could result in better clinical outcomes. Further randomized trials are needed to define the potential benefits of this new treatment modality.

Key Words: Hemoadsorption; Sepsis; Cytokines; Clinical conditions; Inflammation and extracorporeal

Core tip: CytoSorb® is a promising new extracorporeal cytokine hemoadsorption device that can modulate the cytokine storm during sepsis. This retrospective study evaluated clinical outcomes after CytoSorb® therapy of 100 patients admitted to intensive care unit with sepsis. We observed a significant reduction in vasopressors dosage in 40 patients who survived. The survivors also had a reduction in all the biomarker levels (procalcitonin, C-reactive protein, serum lactate and bilirubin) and inflammatory markers (interleukin 6, interleukin 10 and tumour necrosis factor) after CytoSorb® therapy. Notably, 28% of patients who were given CytoSorb® therapy < 48 h after onset of septic shock survived.

Citation: Mehta Y, Mehta C, Kumar A, George JV, Gupta A, Nanda S, Kochhar G, Raizada A. Experience with hemoadsorption (CytoSorb®) in the management of septic shock patients. *World J Crit Care Med* 2020; 9(1): 1-12
URL: https://www.wjgnet.com/2220-3141/full/v9/i1/1.htm
DOI: https://dx.doi.org/10.5492/wjccm.v9.i1.1

INTRODUCTION

Sepsis results due to complex interactive reactions between infecting microbe and the immune system of host. In patients admitted to intensive care units (ICU), sepsis is a major health problem worldwide and is associated with high mortality rates. Approximately, 30% of patients admitted to ICU have sepsis[1]. If not managed properly, sepsis can result in septic shock, systemic hyper inflammation and multiple organ failure[2]. Use of inappropriate antibiotics, virulence of bacteria and host response aggravates the activation of the inflammatory response which leads to dysregulation of inflammatory homeostasis with increased levels of both pro-inflammatory [interleukin (IL)-1β and tumour necrosis factor (TNF) α] and anti-inflammatory (IL-6, IL-8, IL-10) plasma mediators[3]. It results in major complications such as hypotension, reduced organ perfusion, need of organ support system like dialysis and mechanical ventilation[4,5].

Various extracorporeal blood purification therapies have been used to remove excess of inflammatory mediators or microbial toxins to improve health outcomes of patients with severe sepsis. Assuring results are obtained by various techniques including hemoperfusion, immunoglobulin therapy, endotoxin- binding polymyxin B hemoperfusion, high-volume hemofiltration, high cut-off membrane hemofiltration /hemodialysis, plasma exchange, and coupled plasma filtration adsorption dialysis and plasma filtration etc. However, the mortality rate still remains high with these techniques as observed in the recent EUPHRATES trial[6-9].

CytoSorb® is an European CE mark approved and ISO certified hemoadsorption device which helps in reduction of excess inflammatory cytokines in the blood[10,11]. This unique therapy can eliminate bacterial exotoxins, myoglobin, free hemoglobin, bilirubin, activated complement and hosts of other inflammatory agents which can lead to fatal systemic inflammatory response syndrome (SIRS)[11]. Its clinical utility is also observed in various other clinical conditions including cardiac surgeries, liver failure, respiratory failures and various autoimmune diseases and infections[11-13].

In previous studies, CytoSorb® therapy has shown clinical benefits if used early (< 24 h) in patients with septic shock[14,15]. The aim of the present study was to evaluate the clinical outcomes after CytoSorb® therapy in patients admitted to ICU with septic

shock due to different clinical conditions.

MATERIALS AND METHODS

Study design

This retrospective and observational study was conducted at Medanta medicity, Gurgaon, India for duration of 2 years (2016-2018). The study was approved by an institutional ethics committee and conducted in compliance with the current International Council for Harmonization, good clinical practice, Schedule Y, and Indian Council of Medical Research guidelines. A written informed consent was obtained from all patients' relatives before initiating the therapy. The patients/caretakers were briefed about the usage, advantages and disadvantages of treatment. CytoSorb® is a whole blood perfusion cartridge meant for single use. It is made up of biocompatible, polystyrene and divinylbenzene polymer beads with a large surface area. It can be easily used in conjunction with various renal replacement therapies and as a standalone therapy as well. The cartridge is attached in a close loop circuit with a pump. Venous blood of the patient enters at one end of the hemadsorption cartridge, and reinfused from the other port of dialysis catheter. It can be used maximum for 24 h. It removes hydrophobic molecules between 5-60 Kda by adsorption. Molecules beyond this range remain unaffected. Its use may be challenging in patients with contraindication to systemic anticoagulation. It is associated with decrease in platelet levels, though this has not been found to be clinically significant[12].

Study characteristics

Inclusion/exclusion criteria: The medical records of the patients who had received CytoSorb® therapy following diagnosis of sepsis or septic shock (as per the surviving sepsis guidelines) and hospitalized in ICU between 2016 and 2018 were included. We selected the patients with acute kidney injury and sepsis for dialysis and CytoSorb® combination therapy.

Evaluation of application of CytoSorb® scoring system for patient selection to start the therapy: We retrospectively evaluated the application of the CytoSorb® scoring (CS) system developed by a group of clinicians for initiating CytoSorb® therapy on the basis of their practical experience. The scoring system was derived from five parameters (hemodynamic, renal, respiratory, laboratory and sepsis scores), representing five different organ system which get affected in sepsis patients. At the end, final scores were calculated by adding all the individual organ system scores. Supplementary Table 1 presents the CS system. Scores of 8-13 were considered ideal for recommending CytoSorb® therapy. Scores > 13 implied that the patient condition was critical and required aggressive therapy.

Study procedure

Evaluation of laboratory and vital parameters: Baseline patient data including relevant demographic details, vitals, clinical diagnosis were recorded in the case record form. The related laboratory tests for renal, liver and metabolic parameters were evaluated in both pre and post CytoSorb® therapy and a comparison was done between the survivor and the non-survivor group. All the laboratory parameters' limits (values) were categorized as per the scoring system (Supplementary Table 1). Routine ICU monitoring parameters were also noted like routine biochemical investigations, and clinical parameters like Glasgow Coma Scale (GCS). GCS is a neurological scale used as a part of several ICU scoring systems for assessment of central nervous system.

Vasopressors dose and hemodynamic parameters: We compared the mean arterial pressure (MAP) improvement and vasopressor dose (percentage reduction) between pre and post CytoSorb® therapy among survivors and non-survivors. Post therapy, the percentage decrease in number of patients needing both reduced number and doses of vasopressor drugs, *i.e.*, norepinephrine (NE), epinephrine (E), and vasopressin (V) was evaluated.

Evaluation of other outcomes: Inflammatory parameters including interleukins; IL1, IL6, IL10, TNF and sequential organ failure assessment (SOFA) score were recorded pre and post therapy. Acute physiology and chronic health evaluation (APACHE II) were also recorded. Survival outcomes were determined on the basis of time taken (<

48 h or > 48 h) to initiate CytoSorb® therapy after admitting in ICU. Length of patients' stay in ICU (total number of days spent by the patient in ICU before, during and post CytoSorb® therapy) was also recorded. Predicted percentage mortality calculated using APACHE-II calculator was used as a severity score and mortality estimation tool[16].

Statistical analysis

The continuous data were presented as mean ± SD and categorical as frequency and percentage (%). The analysis was performed using paired *t* test. $P < 0.05$ was considered to be statistically significant.

RESULTS

Study population

A total of 100 patients were included in the study. The mean age of all the patients was 52.53 ± 16.46 years. Majority of the patients were men (77.0%) with mean age of 51.33 ± 17.11 years. The mean age of women patients was 56.52 ± 13.62 years. Of these 100 patients, 40 (40%) patients survived (survivor group). The baseline characteristics of all the patients in both the groups are presented in Table 1.

Study outcomes

Effect of CytoSorb® therapy on vasopressor dose and MAP levels: In the survivor group, an improvement in post CytoSorb® therapy MAP (68.23 ± 7.50 mmHg) as compared to pre CytoSorb® MAP (62.82 ± 9.73 mmHg; $P = 0.1805$) was observed.

We also observed a reduction in doses of E (post CytoSorb® therapy: 12.76 ± 7.36 mcg/ min *vs* pre CytoSorb® therapy: 19.38 ± 9.91 mcg/ min; $P = 0.0816$), NE (post CytoSorb® therapy: 14.04 ± 10.46 mcg/ min *vs* pre CytoSorb® therapy: 17.68 ± 15.45 mcg/min; $P = 0.3099$) and V (post CytoSorb® therapy: 1.33 ± 0.93 mcg/min *vs* pre CytoSorb® therapy: 2.01 ± 1.13 mcg/min; $P = 0.0678$).

In the non-survivor group, there was no improvement in MAP (64.31 ± 10.88 mmHg *vs* 66.31 ± 9.48 mmHg) post CytoSorb® therapy *vs* pre post CytoSorb® therapy. Further, no reduction in vasopressor dose was reported post CytoSorb® therapy. Figure 1 shows the comparison of mean percentage reduction in doses of vasopressor drugs for the patients in the survivor and non-survivor groups.

Evaluation of CytoSorb scores and number of CytoSorb® devices required: Prior to CytoSorb® therapy, majority of the patients were on dialysis and continued to be on dialysis post therapy. In the survivor group, patients were on different types of dialysis treatment CRTT ($n = 42$), HD ($n = 24$) and SLED ($n = 34$). The number of CytoSorb® devices used per patient varied between 1-3.

Using the clinicians' designed scoring system for initiation of CytoSorb® therapy, we tried to retrospectively validate this scoring system in our patients. Through this scoring system, we observed that the patients in the survivor group had mean score of 12 as compared to those in the non-survivor group with mean score of 14. Patients with CytoSorb (CS) scores of 10 and 11 had mostly received one CytoSorb® device. Overall, there were 79 patients (32 from survivor and 47 from non-survivor group) with high CS score (12-14) and were recommended more than one CytoSorb® device. Only one patient each with CS score 13 and CS score 14 were recommended 3 CytoSorb® devices. The correlation of CS scores with number of devices recommended for both the groups is shown in Table 2.

Effect of CytoSorb® therapy on laboratory and vital parameters: In the survivor group, 16% decrease (from 15.60 ± 8.56 cells/mm^3 to 13.09 ± 6.71 cells/mm^3, $P = 0.1484$) in total leucocyte count was reported post CytoSorb® therapy. The platelet count decreased slightly by 4.2% (from 123.95 ± 51.42 cells/mm^3 to 118.75 ± 48.33 cells/mm^3, $P = 0.6425$). Serum creatinine and Serum lactate reduced by 17% (from 2.73 ± 1.86 mg/dL to 2.27 ± 1.31 mg/dL, $P = 0.2048$) and 27% (from 3.71 ± 2.30 mg/dL to 2.28 ± 0.89 mg/dL, $P = 0.0159$), respectively. Procalcitonin (PCT) levels reduced by 65% (from 121.56 ± 421.20 ng/dL to 42.80 ± 69.89 ng/dL), C-reactive protein (CRP) levels reduced by 27% (from 165.68 ± 169.26 mg/dL to 120.33 ± 63.72 mg/dL) and bilirubin levels dropped by 43% (from 3.27 ± 2.67 mg/dL to 1.86 ± 1.51 mg/dL, $P = 0.05$).

Improvement was also reported in GCS in the patients in survivor group as compared with patients in the non-survivor group. One patient showed an

Table 1 Baseline characteristics of all the patients, survivors and non-survivors before initiating the therapy (mean ± SD)

Baseline characteristics	Survivors (*n* = 40)	Non-survivors (*n* = 60)	*P* value (survivors *vs* non-survivors)
Age (yr)	51.3 ± 16.66	53.66 ± 16.47	0.4864
Urine output (mL/d)	551.13 ± 524.60	666.48 ± 595.25	0.3224
MAP (mmHg)	62.82 ± 9.73	66.31 ± 9.48	0.0774
GCS	6.26 ± 3.67	6.12 ± 4.56	0.8715
APACHE-II	24.6 ± 7.32	27.61 ± 9.29	0.0881
SOFA	12.3 ± 3.17	15.05 ± 3.35	0.0001
Leucocytes (cells/mm^3)	15.60 ± 8.56	21.40 ± 26.17	0.1794
Platelets (cells/mm^3)	123.95 ± 51.42	110.53 ± 50.18	0.1976
BUN	58.45 ± 36.94	108.55 ± 92.10	0.0015
SGOT(U/L)	1135.74 ± 2206.67	616.25 ± 1353.71	0.1477
SGPT(U/L)	504.63 ± 876.89	540.93 ± 1216.70	0.8712
S. Creatinine (mg/dL)	2.73 ± 1.86	7.01 ± 23.41	0.2521
S. Lactate (mg/dL)	3.71 ± 2.30	4.18 ± 3.23	0.3812
$PaCO_2$	38.46 ± 14.51	40.89 ± 12.20	0.3682
PaO_2	96.78 ± 41.42	84.50 ± 48.56	0.1920
FiO_2	49.32 ± 18.71	69.15 ± 67.74	0.0744

MAP: Mean arterial pressure; GCS: Glasgow coma scale; APACHE: Acute physiology and chronic health evaluation; SOFA: Sequential organ failure assessment; BUN: Blood urea nitrogen; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase.

Table 2 CytoSorb scores and number of Cytosorb® devices used (survivor *vs* non-survivor group)

CS score	Survivor (*n*)	CS score (*n*, number of devices used)	Non-survivor (*n*)	CS score (*n*, number of devices used)
< 8	0	-	0	-
8-13	35	10 (*n* = 1, 1)	21	11 (*n* = 1, 1)
		11 (*n* = 7, 1)		12 (*n* = 6, 1)
		12 (*n* = 19; 18 = 1, 1 = 2)		13 (*n* = 14; 13 = 1, 1 = 3)
		13 (*n* = 8; 1 = 1, 3 = 2, 1 = 3)		
> 13	5	14 (*n* = 5; 1 = 1, 3 = 2, 1 = 3)	39	14 (*n* = 27; 21 = 1, 6 = 2)
				15 (*n* = 12; 11 = 1, 4 = 2)

CS: CytoSorb.

improvement of more than 50% (from score 5 to 10) and one patient showed an improvement of 75% (from score 3 to 12). There was an overall 22.3% (8.05 ± 3.91) improvement in GCS. Slight improvement in other vital parameters like heart rate, respiratory rate, BP and body temperature was also reported.

Among non-survivors, a significant reduction in serum creatinine (25%, $P = 0.008$) was observed. Other laboratory and vital parameters except GCS (30%, $P = 0.0129$) did not show any significant improvement. Change in the laboratory and vital parameters pre and post therapy among survivors and non survivors is shown in Tables 3 and 4.

Cytokine assay

There was a significant reduction in levels of inflammatory markers IL6, IL10 and TNF in the survivor group. A high percentage reduction in IL6 and IL10; (87% and 92%, $P < 0.0001$) and in TNF (24%, $P = 0.0003$) was observed. Among non-survivors, there was no improvement in any of the cytokine levels. Tables 5 and 6 show the cytokine assay data for patients in survivor and non-survivor group

Table 3 Change in laboratory and vital parameters (survivors)

Parameters	Pre CytoSorb® therapy	Post CytoSorb® therapy	Percentage change	*P* value
Urine output (mL/d)	551.13 ± 524.60	862.88 ± 682.46	56.56	0.0247[a]
CRP (mg/dL)	165.68 ± 169.26	120.33 ± 63.72	-27.4	0.6590
PCT (ng/dL)	121.56 ± 421.20	42.81 ± 69.89	-65	0.5859
MAP (mm/Hg)	62.82 ± 9.73	68.23 ± 7.50	8.6	0.1805
GCS	6.26 ± 3.67	8.05 ± 3.92	22.36	0.0417[c]
Leucocytes (cells/mm^3)	15.60 ± 8.56	13.09 ± 6.71	-16.02	0.1484
Platelets (cells/mm^3)	123.95 ± 51.42	118.75 ± 48.33	-4.2	0.6425
S. Creatinine (mg/dL)	2.73 ± 1.86	2.27 ± 1.31	-16.84	0.2048
S. Lactate (mmol/L)	3.71 ± 2.30	2.28 ± 0.89	-26.66	0.0159[a]
SGOT (U/L)	1135.74 ± 2206.67	1078.92 ± 1890.45	-5.00	0.9222
SGPT (U/L)	504.63 ± 876.89	316.59 ± 645.41	-37.26	0.3796
BUN	58.45 ± 36.94	56.67 ± 28.24	-3.05	0.8266
Bilirubin (mg/dL)	3.27 ± 2.67	1.86 ± 1.51	-43.11	0.0565[a]
Sodium (mmol/L)	136.59 ± 24.49	136.31 ± 24.22	-0.20	0.9615
Potassium (mmol/L)	4.22 ± 0.65	3.75 ± 0.56	-11.14	< 0.0001[a]
Albumin (g/L)	2.64 ± 0.58	2.65 ± 0.62	0.38	0.9412
Arterial pH	7.33 ± 0.13	7.37 ± 0.13	0.55	0.1727
Bicarbonate	20.32 ± 4.05	22.825 ± 3.86	12.35	0.0060[a]
PaO_2	96.78 ± 41.42	85.88 ± 27.89	-11.26	0.1714
$PaCO_2$	38.46 ± 14.51	38.36 ± 14.53	-0.26	0.9755
FiO_2	49.32 ± 18.71	41.95 ± 13.71	-14.94	0.0550

[a]*P* < 0.05, significant decrease;
[c]*P* < 0.05, significant rise. All values are defined as mean ± SD. Hb: Haemoglobin; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic-pyruvic transaminase; BUN: Blood urea nitrogen; CRP: C-reactive protein; PCT: Procalcitonin test; MAP: Meanarterial pressure; GCS: Glasgow Coma Scale.

Sepsis scores

Post therapy 16.2% (*P* = 0.0070) fall in SOFA scores was observed in the survivor group. Among non-survivors1% rise in SOFA score, was observed after therapy. Figure 2 shows the change in APACHE II and SOFA scores in both groups for pre and post CytoSorb® therapy.

Predicted percentage mortality

As per APACHEII calculator[16], the mean predicted percentage mortality was 54% (53.68 ± 28.84) for the survivor group and 62% (62.32 ± 29.44) for the non-survivor group.

Survival outcomes: Initiation of therapy after onset of shock and number of days spent in ICU

CytoSorb® therapy was started as per the severity of septic shock and clinical parameters of patients. From an overall pool of patients (*n* = 100), 60 patients were started with CytoSorb® therapy within 48 h of ICU admission and 40 patients more than 48h of ICU admission. We observed that in the survivor group (*n* = 40), 70% (*n* = 28) of patients received CytoSorb® therapy within 48 h of ICU admission as compared to 72% of non survivors (*n* = 43/60) in whom CytoSorb® was initiated after 48 h after ICU admission. Figure 3 and Figure 4 show the patient survival data for both the groups.

Table 4 Change in laboratory and vital parameters (non-survivor group)

Parameters	Pre CytoSorb® therapy	Post CytoSorb® therapy	Percentage change	*P* value
Urine output (mL/d)	666.48 ± 595.25	493.85 ± 433.11	-25.90	0.0718
CRP (mg/dL)	1175.22 ± 126.60	-	-	-
PCT (ng/dL)	24.91 ± 24.51	48.97 ± 57.57	96.58	0.0766
MAP (mm/Hg)	66.13 ± 9.485	64.31 ± 10.87	-2.75	0.3304
GCS	6.12 ± 4.56	4.27 ± 2.91	-30.23	0.0129[a]
Leucocytes (cells/mm^3)	21.40 ± 26.17	20.25 ± 18.25	-5.34	0.7327
Platelets (cells/mm^3)	110.53 ± 50.18	99.67 ± 47.81	-9.83	0.2273
S. Creatinine (mg/dL)	7.01 ± 23.41	5.27 ± 23.19	-24.82	0.0088[a]
S. Lactate (mmol/L)	4.18 ± 3.23	5.05 ± 3.75	17.2	0.1759
SGOT (U/L)	616.25 ± 1353.71	1418.14 ± 2068	130.12	0.0693
SGPT (U/L)	540.93 ± 1216.70	577.38 ± 945.94	6.74	0.9048
BUN	108.55 ± 92.10	95.02 ± 84.83	-12.46	0.4362
Bilirubin (mg/dL)	5.15 ± 14.19	3.84 ± 4.09	-25.44	0.6543
Sodium (mmol/L)	133.79 ± 26.22	139.51 ± 7.32	4.28	0.1244
Potassium (mmol/L)	4.43 ± 1.03	4.15 ± 1.03	-6.32	0.1392
Albumin (g/L)	3.03 ± 1.07	2.85 ± 0.80	-5.94	0.2988
Arterial pH	7.28 ± 0.14	7.22 ± 0.18	-0.82	0.0438
Bicarbonate	24.52 ± 24.21	22.16 ± 22.19	-9.62	0.6560
PaO_2	84.50 ± 48.56	90.42 ± 51.14	7.01	0.5256
$PaCO_2$	40.89 ± 12.20	45.05 ± 33.71	10.17	0.3760
FiO_2	69.15 ± 67.74	62.6 ± 28.61	-9.47	0.5016

[a]*P* < 0.05, significant decrease, all values are defined as mean ± SD. Hb: Haemoglobin; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic-pyruvic transaminase; BUN: Blood urea nitrogen; CRP: C-reactive protein; PCT: Procalcitonin test; MAP: Mean arterial pressure; GCS: Glasgow Coma Scale.

Table 5 Cytokine assay (survivor group) (mean ± SD)

Cytokine (pg)	Pre CytoSorb® therapy	Post CytoSorb® therapy	Percentage decrease	*P* value
IL-1	3.82 ± 3.12	2.97 ± 2.99	22.25	0.2172
IL-6	1962.04 ± 229.09	254.09 ± 223.62	87	< 0.0001[a]
IL-10	293.75 ± 176.28	124.33 ± 73.61	91.7	< 0.0001[a]
TNF	20.82 ± 5.74	15.86 ± 6.11	23.82	0.0003[a]

[a]*P* < 0.05, significant value. IL: Interleukin; TNF: Tumour necrosis factor.

DISCUSSION

In the management of sepsis, it is necessary to stabilize the hemodynamic levels in patients undergoing treatment for septic shock. Resuscitation in septic shock can be rapidly achieved by restoration of perfusion by administration of intravenous fluids, inotropic supports, and vasopressor drugs. It is of utmost importance to maintain the appropriate MAP levels[17]. Some studies have also shown successful and effective results in the treatment of hemodynamics accompanied by a decrease in vasopressor doses with CytoSorb® therapy[14]. For evaluating the hemodynamic parameters, we used multiple vasopressor drugs; NE, E and V in patients with septic shock > 48 h having MAP > 65 mmHg. Post therapy, in the survivor group, we observed

Table 6 Cytokine assay (non-survivor group) (mean ± SD)

Cytokine (pg)	Pre CytoSorb® therapy	Post CytoSorb® therapy	Percentage change	*P* value
IL-1	5.52 ± 2.59	5.79 ± 2.55	4.89	0.7364
IL-6	2273.51 ± 1212.82	2638.24 ± 1518.26	16.04	0.1486
IL-10	296.00 ± 146.4	295.67 ± 112.00	-0.111	0.9894
TNF	19.43 ± 6.07	20.40 ± 6.26	5.00	0.3914

IL: Interleukin; TNF: Tumour necrosis factor.

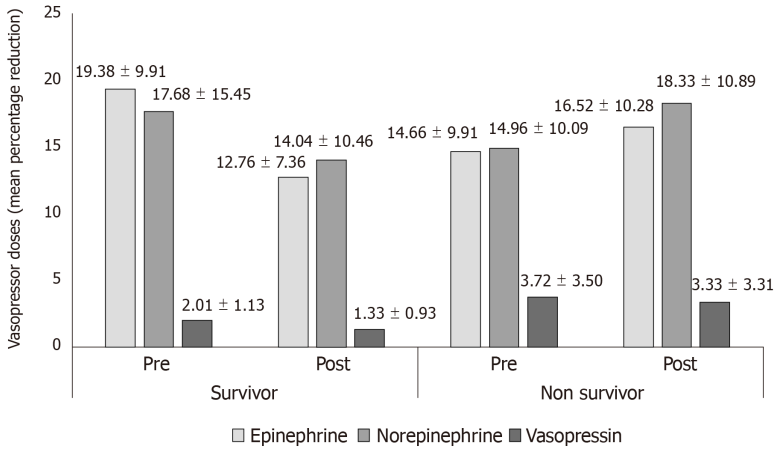

Figure 1 Comparison of percentage reduction in vasopressor doses among survivor and non-survivor patients.

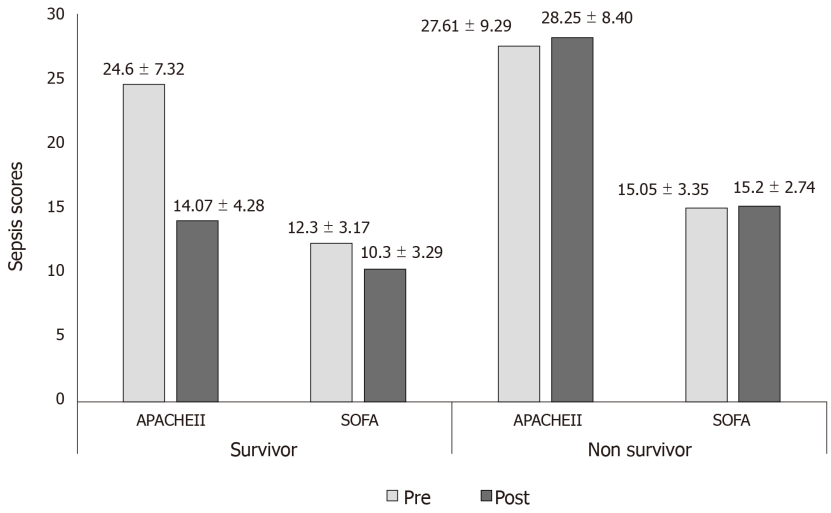

Figure 2 Comparison of sepsis scores among survivor and non-survivor patients. Significant reduction in acute physiology and chronic health evaluation II ($P < 0.0001$) and sequential organ failure assessment ($P = 0.0070$) scores in survivor group. APACHE: Acute physiology and chronic health evaluation; SOFA: Sequential organ failure assessment.

hemodynamic stability with improvement in MAP as compared to pre CytoSorb® therapy. We also observed significant reduction in mean percentage doses of all vasopressors. Post CytoSorb® therapy, the survival rate was 40%. Patients in the survivor group showed better clinical outcomes than non-survivor group in all aspects of laboratory, vital parameters, sepsis scores, cytokine levels and vasopressor needs. A crucial aspect of this study was to look for the patients' suitability for this therapy and to determine the extent of improvement in laboratory and hemodynamic parameters post therapy. Therefore, our clinical team designed a scoring system based on patients' baseline characteristics including five parameters which directly affect the body's main

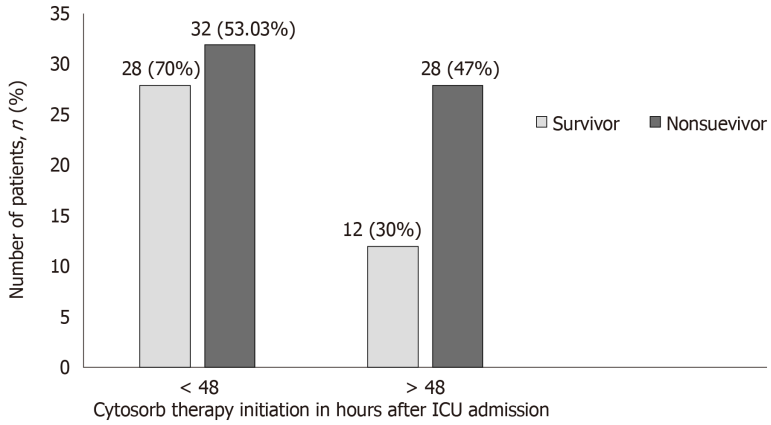

Figure 3 Initiation of CytoSorb® treatment after onset of septic shock. ICU: Intensive care units.

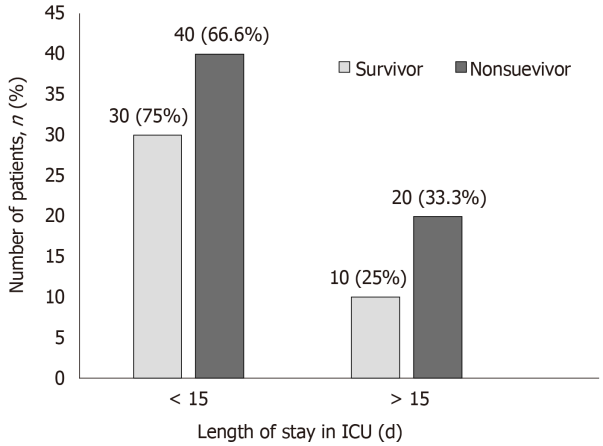

Figure 4 Length of patients' stay in intensive care units (d). ICU: Intensive care units.

organ system that are prone to undergo dysfunction during sepsis (Supplementary Table 1). As per the CS scoring system, CytoSorb® therapy should be recommended to the patients with scores between 8-13. For patients with CS between 10-14, dialysis in combination with one or more CytoSorb® device depending on their clinical outcomes should be followed.

Laboratory parameters such as PCT, CRP and serum lactate are well known biomarkers that indicate cytokine storm[18-20]. We evaluated these parameters considering the target cut off for maximum severity score 3 as PCT (> 3 ng/mL), serum lactate (> 4 mmol) and CRP (> 200 mg/dL). In our study results, we reported remarkable reduction in patients' PCT (65%), CRP (27%), bilirubin (43%, $P = 0.05$), and serum lactate (27%, $P = 0.0159$) levels post CytoSorb® therapy. CytoSorb® device is capable of removing more than 90% bilirubin (0.7 kDa), PCT (13 kDa), and IL-6 (26 kDa)[21,22]. Our study reports were consistent with the study conducted by Hawchar *et al*[23], in 20 patients (CytoSorb® and control group; $n = 10$ each) on mechanical ventilation with baseline PCT > 3 ng/mL and serum lactate > 2.0 mmol/L. CytoSorb® therapy was initiated within 24 h of septic shock and resulted in significant improvement in patients for PCT levels; T_0 = 20.6 [QR: 6.5-144.5] ng/mL, T_{48} = 5.6 [QR: 1.9-54.4] ng/mL, $P = 0.004$. In the control group, PCT levels improved as; T_0 = 13.2 [QR: 7.6-47.8] ng/mL, T_{48} = 9.2 [QR: 3.8-44.2] ng/mL. Serum lactate was reduced by 33% in CytoSorb® group and 53.3% in control group. However, no significant difference was observed in both the groups for CRP concentration. This could be due to high molecular weight of CRP around 25 kDa that might not be absorbed by CytoSorb® as efficiently as PCT. Both groups showed a decrease of CRP by T_{48}[23].

Elevation of proinflammatory cytokines such as TNF and interleukins is a potential marker of the hyper-inflammatory phase of sepsis[20]. In this study, IL6 and IL10 showed significant reduction ($P < 0.0001$) after the therapy in survivor group. Our results were supported by Mitzner and coworkers' study who reported that the use of

CytoSorb® within 24 h in a patient with septic shock and chronic kidney failure decreased the levels of IL-6, CRP, serum creatinine, PCT, and leukocytes during the treatment and in the following days. CytoSorb® hemoadsorber treatment appeared to be safe and was well tolerated by the patient as reported by them[24].

Our study showed a significant improvement in SOFA (P = 0.0070) score in survivor group. Improvement in SOFA scores indicated improvement in clinical condition including laboratory and hemodynamic parameters.

We also studied the correlation between early use of CytoSorb® therapy (< 48 h and > above) with better outcome and evaluated the survival outcomes on the basis of number of days spent in ICU by patients. Two patients were discharged within a day of treatment. Our results were well supported by other studies which reported that use of this therapy within 24h of sepsis diagnosis could lead to decreased mortality in both medical and post-surgical patients[14,15,25].

Overall, the study showed a reduction in the vasopressor dose, a significant reduction in cytokine levels, remarkable reduction in diagnostic markers such as PCT, CRP, bilirubin in and serum lactate after using CytoSorb® therapy. However, the current study has some limitations. First, the present study was a small, single-center retrospective study and underpowered for any significant outcome analysis. Further studies with a larger patient group are needed to deal with this question. Second, the lack of a control group precludes conclusions about effectiveness and cause of the therapy applied. Furthermore appropriate time of initiation of therapy needs to be well defined.

In conclusion, the study showed that the CytoSorb® is a safe and well tolerated rescue therapy option in patients with severe septic shock. However, early (preferably within < 48 h after onset of septic shock) initiation might result in better clinical outcomes. These results may provide important support and guidance to future protocol designs and can help to define the appropriate study end points. Further, prospective randomized controlled trials should be performed to substantiate this hypothesis.

ARTICLE HIGHLIGHTS

Research background

Sepsis is one of the world's leading cause of death in the intensive care unit (ICU) and yet remains the most significant unmet medical need. Sepsis results due to complex interactive reactions between infecting microbe and the immune system of host. CytoSorb® is an European CE mark approved and ISO certified hemoadsorption device which helps in reducing cytokine storm in the blood. In this study, clinical outcomes were evaluated after the use CytoSorb® device as an adjuvant therapy in patients who were admitted in ICU with sepsis between 2016 and 2018.

Research motivation

Most of the patients with septic shock end up dying even though control of inflammation has been attempted through various means. CytoSorb® is an emerging extracorporeal hemadsorption device but there is a paucity of clinical evidence supporting its benefits and clinical outcomes after use. Previous individual studies have shown promising results after use of CytoSorb® therapy in patients with sepsis and septic shock. We used CytoSorb® in 100 patients admitted to ICU with sepsis a rescue therapy but had not analyzed the data to evaluate clinical outcomes in these patients. This study will serve as an important link to guide doctors about the usage of CytoSorb® and possible clinical outcomes. Further, this study will help answer an important question of when to start the CytoSorb® therapy after the onset of septic shock and how many devices are optimums for patients.

Research objectives

The objective of this study was to evaluate the clinical benefits of CytoSorb® therapy in critically ill patients admitted in ICU. We looked for the patients' suitability for this therapy and determined the extent of improvement in laboratory and hemodynamic parameters post therapy with CytoSorb®. Future research should have the objective of a comparative study with a control group and a prospective randomized controlled trial should be performed to provide more evidence.

Research methods

A retrospective observational study was carried out over a period of 2 years. We used the CytoSorb® scoring (CS) system that was developed by group of clinicians for initiating CytoSorb® therapy on the basis of their practical experience for the evaluation of patients. The scoring system was derived from five parameters (hemodynamic, renal, respiratory, lab and sepsis scores), representing five different organ system which get affected in sepsis patients. At the end, final scores were calculated by adding all the individual organ system scores. We evaluated the vitals, laboratory and other parameters by observing the data pre and post CytoSorb® administration.

Research results

The survivor group had a decrease in total leucocyte count, serum creatinine, serum lactate and platelet count. In the non-survivor group, serum creatinine levels and other parameters did not improve. We also observed that there was a significant decrease in inflammatory markers in the survivor group. Another major observation is that 70% of those who received the CytoSorb® therapy within 48 h had better chances of survival.

Research conclusions

CytoSorb® score used in this study is a newly devised scoring system that can guide doctors about usage of CytoSorb® therapy. This study proposes that the CytoSorb® therapy should be recommended to the patients with scores between 8-13. For patients with CS between 10-14; dialysis in combination with one or more CytoSorb® device depending on their clinical outcomes should be followed. In summary, this study showed a reduction in the vasopressor dose, a significant reduction in cytokine levels, remarkable reduction in diagnostic markers such as PCT, CRP, bilirubin and serum lactate after the usage of CytoSorb® therapy. The new hypothesis that this study proposed is there is an improvement in MAP levels, vasopressor dose and other laboratory and clinical parameters when the CytoSorb® therapy is initiated early after onset of septic shock. We used a newly devised scoring system called CytoSorb® score that was derived from five parameters (hemodynamic, renal, respiratory, laboratory and sepsis scores), representing five different organ system which get affected in sepsis patients. Through this study, we reinforced that the CytoSorb® is a safe and well tolerated rescue therapy option in patients with severe septic shock.

Research perspectives

The lesson learnt from this study is that CytoSorb® therapy should be initiated early in critically ill patients with sepsis and septic shock. In the future, we should design randomized clinical studies that can compare the results with control population. The best method would be to use CS score to decide the usage of CytoSorb® therapy.

ACKNOWLEDGEMENTS

The authors acknowledge Mr. Pradeep Yanamala for end to end coordination and extended support in formatting of this paper and in that line improved the manuscript significantly and Knowledge Isotopes Pvt. Ltd (https://www.knowledgeisotopes.com) for the medical writing assistance.

REFERENCES

1 **Sakr Y**, Jaschinski U, Wittebole X, Szakmany T, Lipman J, Ñamendys-Silva SA, Martin-Loeches I, Leone M, Lupu MN, Vincent JL; ICON Investigators. Sepsis in Intensive Care Unit Patients: Worldwide Data From the Intensive Care over Nations Audit. *Open Forum Infect Dis* 2018; **5**: ofy313 [PMID: 30555852 DOI: 10.1093/ofid/ofy313]

2 **Genga KR**, Russell JA. Update of Sepsis in the Intensive Care Unit. *J Innate Immun* 2017; **9**: 441-455 [PMID: 28697503 DOI: 10.1159/000477419]

3 **Schulte W**, Bernhagen J, Bucala R. Cytokines in sepsis: potent immunoregulators and potential therapeutic targets--an updated view. *Mediators Inflamm* 2013; **2013**: 165974 [PMID: 23853427 DOI: 10.1155/2013/165974]

4 **Sander M**, von Heymann C, von Dossow V, Spaethe C, Konertz WF, Jain U, Spies CD. Increased interleukin-6 after cardiac surgery predicts infection. *Anesth Analg* 2006; **102**: 1623-1629 [PMID: 16717298 DOI: 10.1213/01.ane.0000215998.21739.48]

5 **Donadello K**, Polati E. Hemadsorption in cardiac surgery: myth against reality. *Minerva Anestesiol* 2019; **85**:

697-700 [PMID: 30762328 DOI: 10.23736/S0375-9393.19.13516-X]
6 **Cruz DN**, Antonelli M, Fumagalli R, Foltran F, Brienza N, Donati A, Malcangi V, Petrini F, Volta G, Bobbio Pallavicini FM, Rottoli F, Giunta F, Ronco C. Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. *JAMA* 2009; **301**: 2445-2452 [PMID: 19531784 DOI: 10.1001/jama.2009.856]
7 **Kreymann KG**, de Heer G, Nierhaus A, Kluge S. Use of polyclonal immunoglobulins as adjunctive therapy for sepsis or septic shock. *Crit Care Med* 2007; **35**: 2677-2685 [PMID: 18074464]
8 **Bellomo R**, Baldwin I, Ronco C. Extracorporeal blood purification therapy for sepsis and systemic inflammation: its biological rationale. *Contrib Nephrol* 2001; 367-374 [PMID: 11395904 DOI: 10.1159/000060105]
9 **Klein DJ**, Foster D, Schorr CA, Kazempour K, Walker PM, Dellinger RP. The EUPHRATES trial (Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic shock): study protocol for a randomized controlled trial. *Trials* 2014; **15**: 218 [PMID: 24916483 DOI: 10.1186/1745-6215-15-218]
10 **Shum HP**, Yan WW, Chan TM. Extracorporeal blood purification for sepsis. *Hong Kong Med J* 2016; **22**: 478-485 [PMID: 27538388 DOI: 10.12809/hkmj164876]
11 **Hyde RA**, Ishikawa MY, Jung EKY, Langer R, Leuthardt EC, Myhrvold NP, Sweeney EA, Wood JR LL. Device, system, and method for controllably reducing inflammatory mediators in a subject. America: TVPP, 2009
12 **Bonavia A**, Groff A, Karamchandani K, Singbartl K. Clinical Utility of Extracorporeal Cytokine Hemoadsorption Therapy: A Literature Review. *Blood Purif* 2018; **46**: 337-349 [PMID: 30176653 DOI: 10.1159/000492379]
13 **Hassan K**, Kannmacher J, Wohlmuth P, Budde U, Schmoeckel M, Geidel S. Cytosorb Adsorption During Emergency Cardiac Operations in Patients at High Risk of Bleeding. *Ann Thorac Surg* 2019; **108**: 45-51 [PMID: 30684482 DOI: 10.1016/j.athoracsur.2018.12.032]
14 **Kogelmann K**, Jarczak D, Scheller M, Drüner M. Hemoadsorption by CytoSorb in septic patients: a case series. *Crit Care* 2017; **21**: 74 [PMID: 28343448 DOI: 10.1186/s13054-017-1662-9]
15 **Friesecke S**, Stecher SS, Gross S, Felix SB, Nierhaus A. Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study. *J Artif Organs* 2017; **20**: 252-259 [PMID: 28589286 DOI: 10.1007/s10047-017-0967-4]
16 **Knaus WA**, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**: 818-829 [PMID: 3928249]
17 **Manohar V**, Raj S, Sreekrishnan T, Kumar GK. Cytokine hemoadsorption therapy-An adjuvant in the management of septic shock with multi-organ dysfunction: A case report. *Nat J Physiol Pharm Pharmacol* 2018; **8**: 297-9 [DOI: 10.5455/njppp.2018.8.0728118082017]
18 **Riedel S**. Procalcitonin and the role of biomarkers in the diagnosis and management of sepsis. *Diagn Microbiol Infect Dis* 2012; **73**: 221-227 [PMID: 22704255 DOI: 10.1016/j.diagmicrobio.2012.05.002]
19 **Trásy D**, Molnár Z. Procalcitonin - Assisted Antibiotic Strategy in Sepsis. *EJIFCC* 2017; **28**: 104-113 [PMID: 28757818]
20 **Faix JD**. Biomarkers of sepsis. *Crit Rev Clin Lab Sci* 2013; **50**: 23-36 [PMID: 23480440 DOI: 10.3109/10408363.2013.764490]
21 **Faltlhauser A**, Kullmann F. Use of Hemoadsorption in a Case of Severe Hepatic Failure and Hyperbilirubinemia. *Blood Purif* 2017; **44**: 98-99 [PMID: 28355595 DOI: 10.1159/000470826]
22 **Singh A**, Mehta Y, Trehan N. Bilirubin Removal Using CytoSorb Filter in a Cardiac Surgical Patient. *J Cardiothorac Vasc Anesth* 2019; **33**: 881-883 [PMID: 30292390 DOI: 10.1053/j.jvca.2018.08.213]
23 **Hawchar F**, László I, Öveges N, Trásy D, Ondrik Z, Molnar Z. Extracorporeal cytokine adsorption in septic shock: A proof of concept randomized, controlled pilot study. *J Crit Care* 2019; **49**: 172-178 [PMID: 30448517 DOI: 10.1016/j.jcrc.2018.11.003]
24 **Mitzner SR**, Gloger M, Henschel J, Koball S. Improvement of hemodynamic and inflammatory parameters by combined hemoadsorption and hemodiafiltration in septic shock: a case report. *Blood Purif* 2013; **35**: 314-315 [PMID: 23920222 DOI: 10.1159/000351206]
25 **Träger K**, Fritzler D, Fischer G, Schröder J, Skrabal C, Liebold A, Reinelt H. Treatment of post-cardiopulmonary bypass SIRS by hemoadsorption: a case series. *Int J Artif Organs* 2016; **39**: 141-146 [PMID: 27140295 DOI: 10.5301/ijao.5000492]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 2220-3141 (online)

World Journal of *Critical Care Medicine*

World J Crit Care Med 2020 June 5; 9(2): 13-42

Published by Baishideng Publishing Group Inc

World Journal of Critical Care Medicine

Contents

Irregular Volume 9 Number 2 June 5, 2020

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Study

Observational Study

Contents

World Journal of Critical Care Medicine

Volume 9 Number 2 June 5, 2020

ABOUT COVER

Editorial Board Member of *World Journal of Critical Care Medicine*, Caterina Aurilio, MD, Full Professor, Department of Woman, Child and General and Specialized Surgery, University of Campania L. Vanvitelli, Napoli 80139, Italy

AIMS AND SCOPE

The primary aim of the *World Journal of Critical Care Medicine* (*WJCCM*, *World J Crit Care Med*) is to provide scholars and readers from various fields of critical care medicine with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCCM mainly publishes articles reporting research results and findings obtained in the field of critical care medicine and covering a wide range of topics including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, ICU management and treatment control, infection and anti-infection treatment, rational nutrition and immunomodulation in critically ill patients, sedation and analgesia, severe infection, and shock and multiple organ dysfunction syndrome.

INDEXING/ABSTRACTING

The *WJCCM* is now indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yun-Xiaojian Wu*

Proofing Production Department Director: *Xiang Li*

Responsible Editorial Office Director: *Jia-Ping Yan*

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Irregular

EDITORS-IN-CHIEF
KLE Hon

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

PUBLICATION DATE
June 5, 2020

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2020 June 5; 9(2): 13-19

DOI: 10.5492/wjccm.v9.i2.13

ISSN 2220-3141 (online)

MINIREVIEWS

Artificial intelligence and computer simulation models in critical illness

Amos Lal, Yuliya Pinevich, Ognjen Gajic, Vitaly Herasevich, Brian Pickering

ORCID number: Amos Lal (0000-0002-0021-2033); Yuliya Pinevich (0000-0001-9005-8844); Ognjen Gajic (0000-0003-4218-0890); Vitaly Herasevich (0000-0002-0214-0651); Brian Pickering (0000-0002-8307-8449).

Author contributions: All authors equally contributed to this paper.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Manuscript source: Invited manuscript

Received: December 31, 2019
Peer-review started: December 31, 2019
First decision: March 28, 2020
Revised: April 21, 2020
Accepted: May 12, 2020
Article in press: May 12, 2020
Published online: June 5, 2020

P-Reviewer: Cuocolo R, Liu Y

Amos Lal, Ognjen Gajic, Department of Medicine, Division of Pulmonary and Critical Care Medicine, Rochester, Mayo Clinic, MN 55905, United States

Amos Lal, Yuliya Pinevich, Ognjen Gajic, Vitaly Herasevich, Brian Pickering, Multidisciplinary Epidemiology and Translational Research in Intensive Care Group, Mayo Clinic, Rochester, MN 55905, United States

Yuliya Pinevich, Vitaly Herasevich, Brian Pickering, Department of Anesthesiology and Perioperative Medicine, Division of Critical Care, Mayo Clinic, Rochester, MN 55905, United States

Corresponding author: Amos Lal, MBBS, Department of Medicine, Division of Pulmonary and Critical Care Medicine, Multidisciplinary Epidemiology and Translational Research in Intensive Care Group, Mayo Clinic, 200 1st St SW, Rochester, MN 55905, United States. lal.amos@mayo.edu

Abstract

Widespread implementation of electronic health records has led to the increased use of artificial intelligence (AI) and computer modeling in clinical medicine. The early recognition and treatment of critical illness are central to good outcomes but are made difficult by, among other things, the complexity of the environment and the often non-specific nature of the clinical presentation. Increasingly, AI applications are being proposed as decision supports for busy or distracted clinicians, to address this challenge. Data driven "associative" AI models are built from retrospective data registries with missing data and imprecise timing. Associative AI models lack transparency, often ignore causal mechanisms, and, while potentially useful in improved prognostication, have thus far had limited clinical applicability. To be clinically useful, AI tools need to provide bedside clinicians with actionable knowledge. Explicitly addressing causal mechanisms not only increases validity and replicability of the model, but also adds transparency and helps gain trust from the bedside clinicians for real world use of AI models in teaching and patient care.

Key words: Artificial intelligence; Digital twin; Critical illness; Predictive enrichment; Causation; Simulation models

Core tip: Widespread implementation of electronic health records coupled with increased

S-Editor: Ma YJ
L-Editor: A
E-Editor: Wu YXJ

computer power has led to the increased use of artificial intelligence and computer modeling in clinical medicine. To be clinically useful, artificial intelligence models need to be built on accurate data, take into consideration causal mechanisms, and provide actionable information at the point of care.

Citation: Lal A, Pinevich Y, Gajic O, Herasevich V, Pickering B. Artificial intelligence and computer simulation models in critical illness. *World J Crit Care Med* 2020; 9(2): 13-19
URL: https://www.wjgnet.com/2220-3141/full/v9/i2/13.htm
DOI: https://dx.doi.org/10.5492/wjccm.v9.i2.13

INTRODUCTION

The complex nature of critical illness calls for an exploration of alternative approaches to assist clinicians in their timely diagnosis and management. Artificial intelligence (AI) applications have transformed various human domains from economics to traffic and have recently been introduced into health care.

AI IN HEALTH CARE

Widespread implementation of electronic health records (EHRs) has led to the increased use of AI and computer modeling in clinical medicine. The hope is that these techniques will prove superior to traditional epidemiologic and statistical approaches and will unlock insights that lead to the development of new treatment recommendations and prediction models. AI can be defined as the field of computer science that enables computers to perform the human cognitive tasks[1]. The interest in AI and systems science methodologies in the research community has grown rapidly in recent years[2]. Specific AI applications of interest to critical care include machine and deep learning algorithms, "in silico" simulation models, and "digital twins".

Machine learning

Machine learning (ML) is an application of AI that develops statistical analysis models using computational technologies applied to big data[3]. The following learning techniques could be used: (1) Supervised learning techniques include but are not limited to linear regression, decision trees, and Naive Bayes. The models developed based on these are normally used for anomaly detection with the use of algorithm approximating a known output with a higher accuracy from a labeled data set, for example: Electrocardiogram interpretation by the automated machine or detection of a lung nodule from a chest X ray or a CT scan based on pattern recognition[4,5]. The aim of models developed using this technique is to decipher rules and latent relationships within data. "Support Vector Machine" is an example of supervised ML algorithm which is used for both classification and regression challenges and give a different dimension to the ensemble models. They are crucial in cases which require high predictive power but these algorithms are hard to visualize due to the complexity in formulation; (2) Unsupervised learning: Unsupervised ML models are developed using clustering techniques which includes segmenting data by some shared attributes, detecting anomalies that do not fit to any group and simplifying datasets by aggregating variables with similar attributes. The main goal is to study and determine the intrinsic and often hidden structure of the data. These models use algorithms on unlabeled data with no outputs to predict but are exploratory and intend to find naturally occurring patterns within the data[6]. This technique can be condensed in two major types of problems that unsupervised ML models try to solve, clustering and dimensionality reduction; (3) Semi-supervised learning uses a dataset with unlabeled as well as labeled data to increase the learning precision and appropriate prediction of label function. Further the model is trained and retrained with the estimated labels from the previous step[7]. These semi-supervised ML models are commonly used in medicine such as in voice recognition (medical dictation applications), data mining, and video surveillance (used in e-ICUs)[8,9]; and (4) Reinforcement learning: Reinforcement ML algorithms learn by observing the result of an action taken by the algorithm and applying a similar algorithm where the data are limited or missing[10]. The algorithm iteratively learns from previous response (reward or penalty) and acts with a goal to receive maximum reward in the future.

Deep learning

Deep learning (DL) refers to the automatic determination and processing of the parameters in a network, on the basis of experience. DL is a ML technique that is designed with multiple layers of neurons, including input and output layers, and so-called "hidden layers"[11]. This idea of hidden layers (neural network) is inherited from a popular engineering and cognitive science topic since the 1980s[12,13]. The input data is passed through the layers, and the complexity of output function increases from layer to layer. In the recent past, the use of DL models in medicine has introduced the idea of data analytic modeling from expert-driven feature to data-driven feature. Large and complex databases (with longitudinal event sequences and continuous data points) have made it possible to train complex DL models. These models developed from large and complex databases with multiple hidden neural layers provide limited transparency to the users and are aptly described as "black box" models. The user of "black box" AI knows inputs and understands outcomes of the model, but how the output value was generated is unknown. These DL models are most commonly utilized in the field of medicine for following categories of analytical tasks: (1) Disease detection or classification, where DL models are used to detect a specific disease(s) with the help of data mining from EHR[14]; (2) Sequential prediction of clinical events, where DL models predict future clinical events learning from the previous event sequences[15]; (3) Concept embedding, where DL models derive feature representation of clinical concepts algorithmically from the EHR data[16]; (4) Data augmentation, where DL models create realistic data elements for the use in clinical research or otherwise based on real EHR data[17]; and (5) EHR data privacy, where DL models derive techniques to protect patient EHR privacy by de-identification[18].

In simpler words, it would be easier to understand the relationship of AI, ML and DL by visualizing them as 3 concentric circles with DL being the innermost circle which is a subset of ML. ML in turn is a part of the greater all-encompassing concept of AI (thus AI fits inside both ML and DL).

In silico simulation models and digital twins

"In silico" experimentation or simulation involves mathematical and computer based exemplifications to construct models[19]. Computer based experiments can then be carried out to conduct investigations of hypotheses in a virtual environment without actually involving human subjects. The Archimedes model illustrates the use of mathematical techniques to reproduce the complex nature of disease[20]. The core model is a set of ordinary differential equations, which represent the physiologic, clinical, and social pathways that are relevant to diabetes and diabetes-related complications. The use of causal pathways (*i.e*., Disease Acyclic Graphs) distinguishes Archimedes from conventional, associative AI models[17]. Digital twin is a type of simulation model that combines current data from the object with its simulation model to enhance insight and assist with decision making[21,22]. The digital twin has proven to be effective in industry and transportation, such as gas turbine fleet, rail fleet, and production line. The advantage of this approach is the ability to get the representative operational updates from the real-world object that allows model to give an accurate prediction and to give the feedback to the real-world state directly to make operational changes.

AI IN CRITICAL CARE

Critical illness offers a number of advantages for the developers of AI models compared to chronic disease, such as the availability of large quantities of qualitative and quantitative data and relatively short trajectory of critical illness to a stable outcome. This results in the possible iterative testing of hypotheses raised by simulation modeling in independent patient cohorts. For example, recently, a group of computer scientists and clinicians from the Imperial College, London, United Kingdom used an AI approach to develop a decision support model aptly named AI Clinician[23]. Using reinforcement learning (RL), AI Clinician is designed to assist with optimal treatment interventions for sepsis in real-time. It was developed and validated in two clinical databases: MIMIC-III and e-ICU research database[24,25]. Similar methodology has recently been applied to the continuous prediction of acute kidney injury (AKI)[26]. Tools that are developed based on the current AI models have low specificity in predicting the intervention points for real life sepsis patients. This is one of the major obstacles faced by AI models for treating the critically ill patients. While most of the currently devised models are based on the retrospective data from the data banks, the accuracy and performance of these algorithms on real-time data

may not achieve the same level. Patient privacy concerns and question of responsibility may preclude rapid integration of AI models into current ICU practice. High heterogeneity of patients and their specific needs could be easily illustrated by managing a patient on mechanical ventilation. "Intelligent" ventilation modes may do more harm than good without thorough supervision by a specialist.

The above examples highlight a new approach to predictive and prognostic analytics in the area of critical care. Although these models yielded clinically plausible results, major shortcomings limit inferences and use in the real world of bedside clinical medicine. First, built exclusively from retrospective EHR data, the models suffer from missing data and imprecise timing (back charting) particularly during the initial, golden hours of critical illness. Not unlike retrospective studies using traditional methods (logistic regression), the output results are only hypothesis raising and require prospective confirmation.

PROGNOSTIC (ASSOCIATIVE) *VS* PREDICTIVE (ACTIONABLE) AI MODELS

While offering marginal improvements in performance over traditional epidemiological or logistic regression approaches, associative AI models generally underperform in the live clinical setting and struggle to breach the threshold of usefulness for most clinicians[27]. Even accurate prognostic enrichment (classifying patients with high or low likelihood of death or AKI) is of limited value to the bedside clinician. For example, the prediction model of AKI does not provide any predictive enrichment with regards to potential intervention[26]. For example, will my patient benefit from a red cell transfusion, or continuous *vs* intermittent renal replacement?

Predicting the risk *vs* the benefit of a particular treatment (*i.e.*, actionable AI) is more difficult. Differences between associative and inquisitive/actionable AI are highlighted in Table 1. In contrast to "black box" associative AI, actionable AI models should explicitly address causal relationships[28]. Directed acyclic graphs – (DAG) approach has been increasingly used to address causal relationships in different research domains[29]. DAGs facilitate integration of expert knowledge into data driven AI models and are well suited for building advanced AI algorithms and simulation models.

Bayesian networks are DAGs whose nodes represent variables in the Bayesian sense: They may be observable quantities, latent variables, unknown parameters or hypotheses. Edges represent conditional dependencies; nodes that are not connected (no path connects one node to another) represent variables that are conditionally independent of each other. Each node is associated with a probability function that takes, as input, a particular set of values for the node's parent variables, and gives (as output) the probability (or probability distribution, if applicable) of the variable represented by the node. Directed acyclic graphical model is a probabilistic graphical model (a type of statistical model) that represents a set of variables and their conditional dependencies – also known as the Bayesian network Model.

Unidirectional arrows of DAGs are based on known causal effects (and prior knowledge) (Figure 1). DAGs enable clear representation and better understanding of the key concepts of exposure, outcome, causation, confounding, and bias. DAGs are built as simple integers of physiology as a basis to building complex patterns for seamless functionality of a simulation model and AI application. One of the advantages of using multiple basic DAGs to build a complex model is that, the model can be easily disassembled as individual components (DAGs) to ensure that the complex model can be better understood and refined as necessary.

CONCLUSION

In a complex critical care environment clinicians are challenged with making decisions with a high degree of uncertainty under time constraints. Data driven associative AI models hold promise for better prognostication and to augment the diagnostic process but thus far have not been proven useful for bedside clinicians. Transparency of the model in terms of analytics and algorithms is important for patient safety and to earn the trust of the treating clinician[30]. Actionable AI models are more challenging to build and require explicit consideration of causal mechanisms. Accurate prediction of the response to treatment or intervention without exposing the patients to potential risks is an ultimate AI challenge for the benefit of patient and clinicians alike.

Table 1 Differences between associative artificial intelligence and actionable artificial intelligence models

Models based on associative artificial intelligence	Models based on actionable artificial intelligence
These applications are built using available historical public or institutional data repositories[26,31,32].	These applications are built more often on the prospectively collected data points, predicting risk *vs* benefit of a particular treatment or intervention[17,30,33,34].
Almost always based on retrospective data[35,36].	Developed using the data points that are collected prospectively in real-time[30,34].
Purely data driven associative models often without explicit consideration of causal pathways[37-39].	These models are developed with an understanding based on the underlying causal pathways, therefore providing greater clinical utility and accuracy[40-42].
Representative examples: Development and validation of a data driven tool to predict sepsis based on vital signs by Mao *et al*[43]. Provides no actionable benefit to the bedside clinician. Similarly, a model developed to predict AKI in a patient based on retrospectively collected dataset from electronic health records by Tomasev *et al*[26]. The model was associated with high false positive alerts (2 false positive alerts for each true alert).	*Representative examples*: Improving the safety of ventilator care by avoiding ventilator-induced lung injury. Electronic algorithm based on near real-time data and notification of bedside providers giving actionable information, developed by Herasevich *et al*[33]. Artificial neural network based model developed for forecasting ICP for medical decision support, by Zhang *et al*[42]. This model provided actionable treatment planning for patients based on the predicted future trends of ICP.

AKI: Acute kidney injury; ICP: Intracranial pressure.

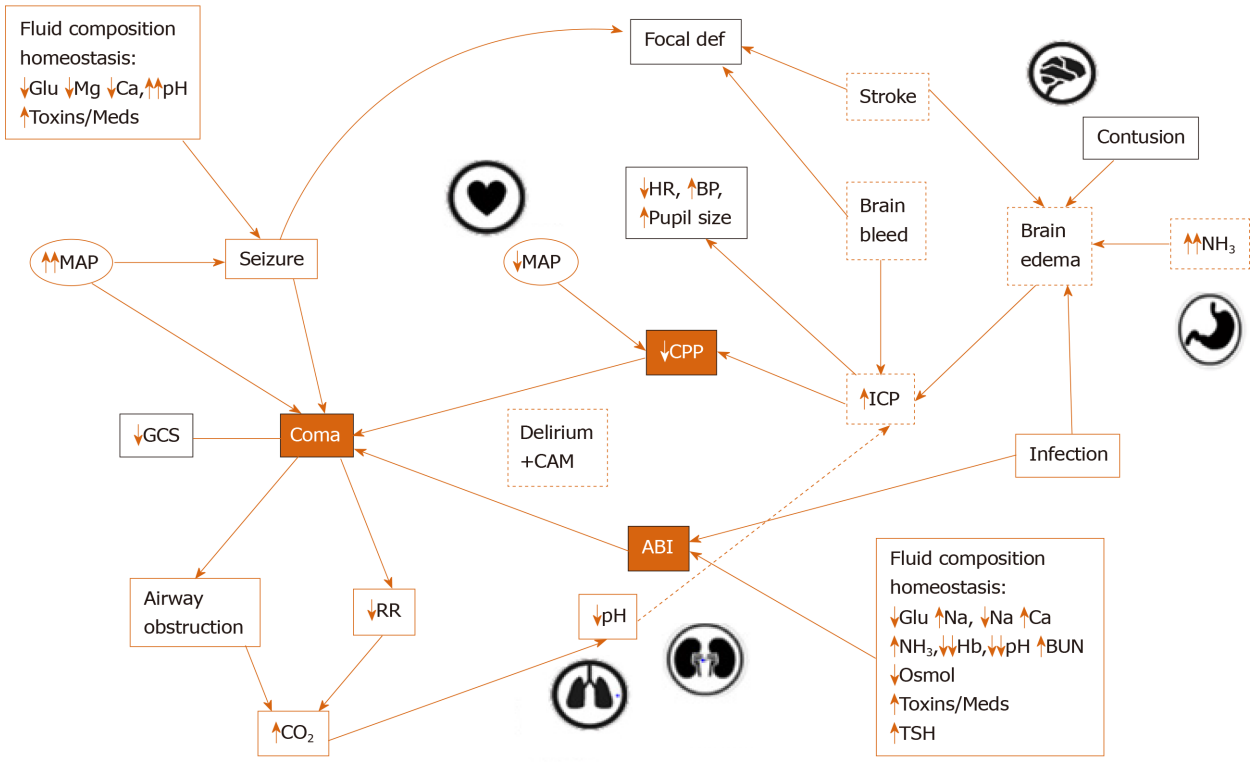

Figure 1 Directed acyclic graph of acute brain failure. Orange boxes: Concepts; Orange solid border: Actionable clinical points; Orange interrupted border: Semi-actionable clinical points. GCS: Glasgow coma scale; MAP: Mean arterial pressure; Glu: Serum glucose; Mg: Serum magnesium; Ca: Serum calcium; Meds: Medications; HR: Heart rate; BP: Blood pressure; Focal Def: Focal neurological deficits; ICP: Intracranial pressure; NH_3: Ammonia; Na: Serum sodium; Hb: Serum hemoglobin; BUN: Blood urea nitrogen; Osmo: Serum osmolality; TSH: Thyroid stimulating hormone; CO_2: Serum carbon dioxide; CPP: Cerebral perfusion pressure; ABI: Acute brain injury; CAM: Confusion assessment method for intensive care unit.

ACKNOWLEDGEMENTS

We thank Mrs Ann Johnson for help with proofreading and language editing of the manuscript.

REFERENCES

1 **Ramesh AN**, Kambhampati C, Monson JR, Drew PJ. Artificial intelligence in medicine. *Ann R Coll Surg*

Engl 2004; **86**: 334-338 [PMID: 15333167 DOI: 10.1308/147870804290]
2 **Gold M**, Beitsch L, Essien J. For the public's health: The role of measurement in action and accountability. National Academies Press website. 2011. Available from: https://www.nap.edu/read/13005
3 **El Naqa I**, Murphy MJ. What Is Machine Learning? What Is Machine Learning? In: El Naqa I, Li R, Murphy M, editors. Machine Learning in Radiation Oncology: Theory and Applications. Cham: Springer International Publishing, 2015: 3-11 [DOI: 10.1007/978-3-319-18305-3_1]
4 **Deo RC**. Machine Learning in Medicine. *Circulation* 2015; **132**: 1920-1930 [PMID: 26572668 DOI: 10.1161/CIRCULATIONAHA.115.001593]
5 **Mathur P**, Burns ML. Artificial Intelligence in Critical Care. *Int Anesthesiol Clin* 2019; **57**: 89-102 [PMID: 30864993 DOI: 10.1097/aia.0000000000000221]
6 **Sidey-Gibbons JAM**, Sidey-Gibbons CJ. Machine learning in medicine: a practical introduction. *BMC Med Res Methodol* 2019; **19**: 64 [PMID: 30890124 DOI: 10.1186/s12874-019-0681-4]
7 **Wongchaisuwat P**, Klabjan D, Jonnalagadda SR. A Semi-Supervised Learning Approach to Enhance Health Care Community-Based Question Answering: A Case Study in Alcoholism. *JMIR Med Inform* 2016; **4**: e24 [PMID: 27485666 DOI: 10.2196/medinform.5490]
8 **Kopec IC**. Impact of Intensive Care Unit Telemedicine on Outcomes. *Crit Care Clin* 2019; **35**: 439-449 [PMID: 31076044 DOI: 10.1016/j.ccc.2019.02.002]
9 **Herasevich V**, Subramanian S. Tele-ICU Technologies. *Crit Care Clin* 2019; **35**: 427-438 [PMID: 31076043 DOI: 10.1016/j.ccc.2019.02.009]
10 **Yom-Tov E**, Feraru G, Kozdoba M, Mannor S, Tennenholtz M, Hochberg I. Encouraging Physical Activity in Patients With Diabetes: Intervention Using a Reinforcement Learning System. *J Med Internet Res* 2017; **19**: e338 [PMID: 29017988 DOI: 10.2196/jmir.7994]
11 **Deng L**, Yu D. Deep learning: methods and applications. *Foundations and Trends® in Signal Processing* 2014; **7**: 197-387
12 **McClelland JL**, Rumelhart DE, Group PR. Parallel distributed processing. Cambridge, MA: MIT Press, 1987
13 **Rumelhart DE**, Mcclelland JL. Parallel distributed processing: Explorations in the microstructure of cognition. Bradford: MIT Press, 1986
14 **Kononenko I**. Machine learning for medical diagnosis: history, state of the art and perspective. *Artif Intell Med* 2001; **23**: 89-109 [PMID: 11470218 DOI: 10.1016/S0933-3657(01)00077-X]
15 **Kaji DA**, Zech JR, Kim JS, Cho SK, Dangayach NS, Costa AB, Oermann EK. An attention based deep learning model of clinical events in the intensive care unit. *PLoS One* 2019; **14**: e0211057 [PMID: 30759094 DOI: 10.1371/journal.pone.0211057]
16 **Xiang Y**, Xu J, Si Y, Li Z, Rasmy L, Zhou Y, Tiryaki F, Li F, Zhang Y, Wu Y, Jiang X, Zheng WJ, Zhi D, Tao C, Xu H. Time-sensitive clinical concept embeddings learned from large electronic health records. *BMC Med Inform Decis Mak* 2019; **19**: 58 [PMID: 30961579 DOI: 10.1186/s12911-019-0766-3]
17 **Eddy DM**, Schlessinger L. Archimedes: a trial-validated model of diabetes. *Diabetes Care* 2003; **26**: 3093-3101 [PMID: 14578245 DOI: 10.2337/diacare.26.11.3093]
18 **Xiao C**, Choi E, Sun J. Opportunities and challenges in developing deep learning models using electronic health records data: a systematic review. *J Am Med Inform Assoc* 2018; **25**: 1419-1428 [PMID: 29893864 DOI: 10.1093/jamia/ocy068]
19 **Viceconti M**, Henney A, Morley-Fletcher E. In silico clinical trials: how computer simulation will transform the biomedical industry. *Inter J Clin Trials* 2016; **3**: 37-46 [DOI: 10.18203/2349-3259.ijct20161408]
20 **Eddy DM**, Schlessinger L, Kahn R. Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes. *Ann Intern Med* 2005; **143**: 251-264 [PMID: 16103469 DOI: 10.7326/0003-4819-143-4-200508160-00006]
21 **Kritzinger W**, Karner M, Traar G, Henjes J, Sihn W. Digital Twin in manufacturing: A categorical literature review and classification. *IFAC-PapersOnLine* 2018; **51**: 1016-1022 [DOI: 10.1016/j.ifacol.2018.08.474]
22 **Anylogic**. An Introduction to Digital Twin Development, White Paper. 2018. Available from: https://www.anylogic.com/resources/white-papers/an-introduction-to-digital-twin-development/
23 **Komorowski M**, Celi LA, Badawi O, Gordon AC, Faisal AA. The Artificial Intelligence Clinician learns optimal treatment strategies for sepsis in intensive care. *Nat Med* 2018; **24**: 1716-1720 [PMID: 30349085 DOI: 10.1038/s41591-018-0213-5]
24 **Johnson AE**, Pollard TJ, Shen L, Lehman LW, Feng M, Ghassemi M, Moody B, Szolovits P, Celi LA, Mark RG. MIMIC-III, a freely accessible critical care database. *Sci Data* 2016; **3**: 160035 [PMID: 27219127 DOI: 10.1038/sdata.2016.35]
25 **Pollard TJ**, Johnson AEW, Raffa JD, Celi LA, Mark RG, Badawi O. The eICU Collaborative Research Database, a freely available multi-center database for critical care research. *Sci Data* 2018; **5**: 180178 [PMID: 30204154 DOI: 10.1038/sdata.2018.178]
26 **Tomašev N**, Glorot X, Rae JW, Zielinski M, Askham H, Saraiva A, Mottram A, Meyer C, Ravuri S, Protsyuk I, Connell A, Hughes CO, Karthikesalingam A, Cornebise J, Montgomery H, Rees G, Laing C, Baker CR, Peterson K, Reeves R, Hassabis D, King D, Suleyman M, Back T, Nielson C, Ledsam JR, Mohamed S. A clinically applicable approach to continuous prediction of future acute kidney injury. *Nature* 2019; **572**: 116-119 [PMID: 31367026 DOI: 10.1038/s41586-019-1390-1]
27 **Christodoulou E**, Ma J, Collins GS, Steyerberg EW, Verbakel JY, Van Calster B. A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models. *J Clin Epidemiol* 2019; **110**: 12-22 [PMID: 30763612 DOI: 10.1016/j.jclinepi.2019.02.004]
28 **Shortliffe EH**, Sepúlveda MJ. Clinical Decision Support in the Era of Artificial Intelligence. *JAMA* 2018; **320**: 2199-2200 [PMID: 30398550 DOI: 10.1001/jama.2018.17163]
29 **Lederer DJ**, Bell SC, Branson RD, Chalmers JD, Marshall R, Maslove DM, Ost DE, Punjabi NM, Schatz M, Smyth AR, Stewart PW, Suissa S, Adjei AA, Akdis CA, Azoulay É, Bakker J, Ballas ZK, Bardin PG, Barreiro E, Bellomo R, Bernstein JA, Brusasco V, Buchman TG, Chokroverty S, Collop NA, Crapo JD, Fitzgerald DA, Hale L, Hart N, Herth FJ, Iwashyna TJ, Jenkins G, Kolb M, Marks GB, Mazzone P, Moorman JR, Murphy TM, Noah TL, Reynolds P, Riemann D, Russell RE, Sheikh A, Sotgiu G, Swenson ER, Szczesniak R, Szymusiak R, Teboul JL, Vincent JL. Control of Confounding and Reporting of Results in Causal Inference Studies. Guidance for Authors from Editors of Respiratory, Sleep, and Critical Care Journals. *Ann Am Thorac Soc* 2019; **16**: 22-28 [PMID: 30230362 DOI: 10.1513/AnnalsATS.201808-564PS]
30 **Ginestra JC**, Giannini HM, Schweickert WD, Meadows L, Lynch MJ, Pavan K, Chivers CJ, Draugelis M,

Donnelly PJ, Fuchs BD, Umscheid CA. Clinician Perception of a Machine Learning-Based Early Warning System Designed to Predict Severe Sepsis and Septic Shock. *Crit Care Med* 2019; **47**: 1477-1484 [PMID: 31135500 DOI: 10.1097/CCM.0000000000003803]

31 **Parreco J**, Hidalgo A, Parks JJ, Kozol R, Rattan R. Using artificial intelligence to predict prolonged mechanical ventilation and tracheostomy placement. *J Surg Res* 2018; **228**: 179-187 [PMID: 29907209 DOI: 10.1016/j.jss.2018.03.028]

32 **Mueller M**, Almeida JS, Stanislaus R, Wagner CL. Can Machine Learning Methods Predict Extubation Outcome in Premature Infants as well as Clinicians? *J Neonatal Biol* 2013; **2** [PMID: 25419493 DOI: 10.4172/2167-0897.1000118]

33 **Herasevich V**, Tsapenko M, Kojicic M, Ahmed A, Kashyap R, Venkata C, Shahjehan K, Thakur SJ, Pickering BW, Zhang J, Hubmayr RD, Gajic O. Limiting ventilator-induced lung injury through individual electronic medical record surveillance. *Crit Care Med* 2011; **39**: 34-39 [PMID: 20959788 DOI: 10.1097/CCM.0b013e3181fa4184]

34 **Giannini HM**, Ginestra JC, Chivers C, Draugelis M, Hanish A, Schweickert WD, Fuchs BD, Meadows L, Lynch M, Donnelly PJ, Pavan K, Fishman NO, Hanson CW, Umscheid CA. A Machine Learning Algorithm to Predict Severe Sepsis and Septic Shock: Development, Implementation, and Impact on Clinical Practice. *Crit Care Med* 2019; **47**: 1485-1492 [PMID: 31389839 DOI: 10.1097/CCM.0000000000003891]

35 **Gao Y**, Xu A, Hu PJH, Cheng TH. Incorporating association rule networks in feature category-weighted naive Bayes model to support weaning decision making. *Decis Support Syst* 2017; **96**: 27-38 [DOI: 10.1016/j.dss.2017.01.007]

36 **Rojas JC**, Carey KA, Edelson DP, Venable LR, Howell MD, Churpek MM. Predicting Intensive Care Unit Readmission with Machine Learning Using Electronic Health Record Data. *Ann Am Thorac Soc* 2018; **15**: 846-853 [PMID: 29787309 DOI: 10.1513/AnnalsATS.201710-787OC]

37 **Zhang Z**, Ho KM, Hong Y. Machine learning for the prediction of volume responsiveness in patients with oliguric acute kidney injury in critical care. *Crit Care* 2019; **23**: 112 [PMID: 30961662 DOI: 10.1186/s13054-019-2411-z]

38 **Zheng B**, Zhang J, Yoon SW, Lam SS, Khasawneh M, Poranki S. Predictive modeling of hospital readmissions using metaheuristics and data mining. *Expert Sys Appl* 2015; **42**: 7110-120 [DOI: 10.1016/j.eswa.2015.04.066]

39 **Deng X**, Yu T, Hu A. Predicting the Risk for Hospital-Acquired Pressure Ulcers in Critical Care Patients. *Crit Care Nurse* 2017; **37**: e1-e11 [PMID: 28765361 DOI: 10.4037/ccn2017548]

40 **Chen L**, Dubrawski A, Wang D, Fiterau M, Guillame-Bert M, Bose E, Kaynar AM, Wallace DJ, Guttendorf J, Clermont G, Pinsky MR, Hravnak M. Using Supervised Machine Learning to Classify Real Alerts and Artifact in Online Multisignal Vital Sign Monitoring Data. *Crit Care Med* 2016; **44**: e456-e463 [PMID: 26992068 DOI: 10.1097/CCM.0000000000001660]

41 **Li A**, Lewis M, Lebiere C, Sycara K, Khatib SS, Tang Y, Siedsma M, Morrison D, editors. A computational model based on human performance for fluid management in critical care. 2016 IEEE Symposium Series on Computational Intelligence (SSCI); 2002, December 6-9, Athens, Greece [DOI: 10.1109/SSCI.2016.7849888]

42 **Zhang F**, Feng M, Pan SJ, Loy LY, Guo W, Zhang Z, Chin PL, Guan C, King NK, Ang BT. Artificial neural network based intracranial pressure mean forecast algorithm for medical decision support. *Conf Proc IEEE Eng Med Biol Soc* 2011; **2011**: 7111-7114 [PMID: 22255977 DOI: 10.1109/IEMBS.2011.6091797]

43 **Mao Q**, Jay M, Hoffman JL, Calvert J, Barton C, Shimabukuro D, Shieh L, Chettipally U, Fletcher G, Kerem Y, Zhou Y, Das R. Multicentre validation of a sepsis prediction algorithm using only vital sign data in the emergency department, general ward and ICU. *BMJ Open* 2018; **8**: e017833 [PMID: 29374661 DOI: 10.1136/bmjopen-2017-017833]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2020 June 5; 9(2): 20-30

DOI: 10.5492/wjccm.v9.i2.20

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Retrospective Study

Hypotension after intensive care unit drop-off in adult cardiac surgery patients

Sabina Cengic, Muhammad Zuberi, Vikas Bansal, Robert Ratzlaff, Eduardo Rodrigues, Emir Festic

ORCID number: Sabina Cengic (0000-0002-6965-5158); Muhammad Zuberi (0000-0002-4072-2898); Vikas Bansal (0000-0001-6047-5559); Robert Ratzlaff (0000-0002-1496-3727); Eduardo Rodrigues (0000-0003-3070-4634); Emir Festic (0000-0003-2002-4248).

Author contributions: Cengic S, Zuberi M, Bansal V and Festic E contributed to study conception and design; Cengic S, Bansal V, Rodrigues E and Festic E contributed to data acquisition, data analysis and interpretation; Cengic S and Festic E contributed to writing of article and final approval of article; Cengic S, Rodrigues E, Ratzlaff R and Festic E contributed to editing and reviewing of article.

Institutional review board statement: This study was reviewed and approved by the Mayo Clinic Institution Review Board.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: The Authors declare that there is no conflict of interest.

Data sharing statement: No additional data are available.

Sabina Cengic, Muhammad Zuberi, Vikas Bansal, Robert Ratzlaff, Emir Festic, Department of Critical Care Medicine, Mayo Clinic, Jacksonville, FL 32224, United States

Sabina Cengic, Department of General Surgery, Stadtspital Triemli, Zurich 8063, Switzerland

Robert Ratzlaff, Eduardo Rodrigues, Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Jacksonville, FL 32224, United States

Corresponding author: Emir Festic, MD, MSc, Full Professor, Consultant, Department of Critical Care Medicine, Mayo Clinic, 4500 San Pablo Rd S, Jacksonville, FL 32224, United States. festic.emir@mayo.edu

Abstract

BACKGROUND

Hypotension is a frequent complication in the intensive care unit (ICU) after adult cardiac surgery.

AIM

To describe frequency of hypotension in the ICU following adult cardiac surgery and its relation to the hospital outcomes.

METHODS

A retrospective study of post-cardiac adult surgical patients at a tertiary academic medical center in a two-year period. We abstracted baseline demographics, comorbidities, and all pertinent clinical variables. The primary predictor variable was the development of hypotension within the first 30 min upon arrival to the ICU from the operating room (OR). The primary outcome was hospital mortality, and other outcomes included duration of mechanical ventilation (MV) in hours, and ICU and hospital length of stay in days.

RESULTS

Of 417 patients, more than half (54%) experienced hypotension within 30 min upon arrival to the ICU. Presence of OR hypotension immediately prior to ICU transfer was significantly associated with ICU hypotension (odds ratio = 1.9; 95% confidence interval: 1.21-2.98; $P < 0.006$). ICU hypotensive patients had longer MV, 5 (interquartile ranges 3, 15) *vs* 4 h (interquartile ranges 3, 6), $P = 0.012$. The patients who received vasopressor boluses ($n = 212$) were more likely to experience ICU drop-off hypotension (odds ratio = 1.45, 95% confidence interval: 0.98-2.13; $P = 0.062$), and they experienced longer MV, ICU and hospital length of stay ($P < 0.001$, for all).

Manuscript source: Unsolicited manuscript

Received: December 22, 2019
Peer-review started: December 26, 2019
First decision: April 9, 2020
Revised: May 8, 2020
Accepted: May 14, 2020
Article in press: May 14, 2020
Published online: June 5, 2020

P-Reviewer: Liu Y
S-Editor: Tang JZ
L-Editor: A
E-Editor: Xing YX

CONCLUSION
Hypotension upon anesthesia-to-ICU drop-off is more frequent than previously reported and may be associated with adverse clinical outcomes.

Key words: Hypotension; Cardiac surgery; Intensive care; Postoperative care; Care transfer; Drop-off

Core tip: Hypotension is a frequent complication in adult cardiac surgery patients upon intensive care unit admission. This complication has been anecdotally called "anesthesia drop-off syndrome" and we decided to study this retrospectively. Our results suggest that this complication is more frequent than previously reported and that it may be associated with adverse outcomes.

Citation: Cengic S, Zuberi M, Bansal V, Ratzlaff R, Rodrigues E, Festic E. Hypotension after intensive care unit drop-off in adult cardiac surgery patients. *World J Crit Care Med* 2020; 9(2): 20-30
URL: https://www.wjgnet.com/2220-3141/full/v9/i2/20.htm
DOI: https://dx.doi.org/10.5492/wjccm.v9.i2.20

INTRODUCTION

Perioperative hypotension is one of the most common complications after cardiac surgery and this may adversely affect clinical outcomes[1-5]. It is frequently encountered upon intensive care unit (ICU) admission, where patients become hypotensive in the immediate post-operative period, shortly after the arrival from the operating room (OR). This has been anecdotally termed "anesthesia drop-off syndrome". However, data is limited in the literature regarding the actual prevalence of hypotension that develops shortly after the transfer of patients to the ICU after cardiac surgery. One study evaluated the occurrence of hemodynamic instability in the first 2 h post cardiac surgery and the most common complication was found to be hypotension, occurring in 34% of the patients after admission to the ICU[6]. Hypotensive patients usually require administration of vasopressor boluses prior to or during the transfer from the OR to the ICU as a temporizing measure. The hypotension and necessity for use of vasopressors have been previously associated with increased hospital length of stay (LOS) as well as mortality, relative to the patients who maintained hemodynamic stability[7-9].

Given the proposed discrepancy between the clinical occurrence and limited data on rate of hypotension starting shortly after the anesthesia to ICU transfer, we aimed to evaluate its prevalence and also how this may relate to the pertinent clinical outcomes. We hypothesized that the occurrence of initial hypotension in the ICU is more frequent complication among post-cardiac surgery ICU patients than previously reported and that patients who experience this complication will have more adverse clinical outcomes. We also aimed to better assess the association between the occurrence of initial hypotension in the ICU and the use of vasopressor bolus administered immediately prior to or during the transfer from the OR to the ICU.

MATERIALS AND METHODS

We conducted a retrospective study of adult patients undergoing cardiac surgery at a tertiary academic medical center in the United States in the 2-year period (January 1, 2015 to December 31, 2016). We excluded patients who underwent cardiac transplantation or a combination of other solid organ transplantation and the cardiac surgery. The study protocol was approved by the Mayo Clinic Institutional Review Board as a minimal risk study, therefore the need for informed consent had been waived.

The primary independent variable was the development of hypotension within the first 30 min upon transfer from the OR ("ICU hypotension"). As there is no single, generally accepted, definition of hypotension[10] we used one of the common

definitions used in biomedical research: A systolic blood pressure < 90 mmHg or mean arterial pressure < 65 mmHg per arterial catheter tracing. We abstracted demographic and baseline characteristics, comorbidities, including coronary artery disease (CAD), atrial fibrillation, diabetes mellitus (DM), pulmonary hypertension, liver disease, kidney disease, infective endocarditis, immunosuppression; and all pertinent clinical variables including: Vitals, laboratories, type and urgency of surgery, bypass and cross-clamp time (CCT), medications and blood products delivered during the surgery and immediately prior to transfer to ICU, as well as presence of hypotension in the OR ("OR hypotension"). A vasopressor bolus use was abstracted from the electronic chart documentation by the provider. Although the exact doses of vasopressors given were not abstracted, our anesthesiologists mostly use norepinephrine (100 μg) and/or vasopressin (1 unit), and much less frequently epinephrine (10 μg). The primary outcome was hospital mortality and secondary outcomes were duration of mechanical ventilation (MV) in hours, and ICU and LOS in days. All data were manually extracted from an electronic medical record. The anesthesia notes during the surgery were extracted partially from plotted diagrams and partially from nominal data.

Statistical analysis

The continuous variables were reported as median values with interquartile ranges (IQR) and the categorical variables were reported as counts and proportions. We used nonparametric statistical tests; Fisher's exact and Wilcoxon Rank-Sum tests, as applicable. The predictor variables in univariate analyses with a *P* value of less than 0.1 were included in the subsequent multivariate analyses. We used nominal logistic and linear regressions, as appropriate. Statistical significance was considered at *P* value of < 0.05. As we performed analysis mainly for the exploratory purpose, no corrections for multiple comparisons were done. We used JMP 10 Pro statistical software for analysis from SAS (Cary, NC, United States).

RESULTS

Out of 1273 cardiothoracic surgeries performed within the study period, 437 patients underwent non-transplant cardiac surgery and were eligible for our study. Twenty patients were excluded subsequently as they lacked detailed blood pressure recordings, leaving 417 patients for the study analyses (Figure 1). The majority of patients were white (85%), males (73%), of median age 67 years (IQR 59, 73), and with median body mass index (BMI) of 28 (IQR 25, 32). The two most commonly performed surgeries were coronary artery bypass grafting (46%) and valvular surgery (29%). The detailed baseline characteristics are listed in Table 1. The median bypass time (BT) was 116 min (IQR 90, 150) and the median CCT was 80 min (IQR 55, 105). While 76% of all surgeries were elective (pre-scheduled), 24% were either emergent (within 24 h of admission) or urgent (24-72 h after hospital admission). The overall postoperative mortality was 3%. The median MV duration was 4 h (IQR 3, 9), and the median ICU and hospital LOS were 2 (IQR 1, 3) and 7 days (IQR 5, 10), respectively.

ICU hypotension

Total of 227 patients (54%) were found to be hypotensive within 30 min upon transfer to the ICU. Nearly three quarters of the whole cohort did not have OR hypotension immediately prior to transfer to the ICU (Figure 2). Presence of OR hypotension immediately prior to ICU transfer was expectedly associated with ICU hypotension [OR = 1.9; 95% confidence interval (CI): 1.21-2.98; $P < 0.006$]. About two-thirds of patients with preceding OR hypotension continued with ICU hypotension and half of those without preceding OR hypotension developed ICU hypotension upon ICU transfer. Higher BMI, history of DM and CAD were associated with significantly higher unadjusted risk of developing ICU hypotension (Table 2). ICU hypotension was associated with the longer duration of MV in hours: 5 (IQR 3, 15) *vs* 4 (IQR 3, 6), $P = 0.012$. Although statistically significant, the clinical significance appeared to be limited only to the patients in the upper quartile (Table 3). Based on the chart documentation, 212 patients received vasopressor boluses around (immediately prior or during) the transfer to the ICU (Figure 3). The patients who received vasopressor bolus on transfer were somewhat more likely to experience ICU drop-off hypotension (OR = 1.45, 95%CI: 0.98-2.13; $P = 0.062$), although this did not quite reach statistical significance. Of the 212 patients who received bolus, 125 (55%) experienced immediate ICU hypotension. Of these 125 patients with ICU hypotension, 78 did not have preceding OR hypotension and 47 did and continued with ICU hypotension from the OR (OR = 1.78; 95%CI: 0.97-3.26; $P = 0.074$). Of 12 patients who died, 9 received the bolus during the transfer and 3 did not (OR = 2.99; 95%CI: 0.8-11.2; *P* =

Table 1 Basic demographics of the study population, *n* (%)

Basic demographics	Overall	ICU hypotension
Total	417	227
Sex		
Male	305 (73)	172 (76)
Female	112 (27)	55 (24)
Median age (IQR)	67 (59, 73)	67 (58, 74)
Race		
Not disclosed	9 (2)	5 (2)
White	356 (85)	197 (87)
Other	52 (13)	25 (11)
Median BMI (IQR)	28 (25, 32)	29 (26, 33)
Mortality		
Alive	405 (97)	217 (96)
Dead	12 (3)	10 (4)
Type of surgery		
Aortic graft	21 (5)	11 (5)
CABG	193 (46)	113 (50)
Ventriculomyotomy	26 (6)	9 (4)
Valve	122 (29)	63 (28)
Aortic graft + CABG	3 (0.7)	1 (0.4)
Valve + CABG	30 (7)	23 (10)
ASD repair	7 (2)	4 (2)
Aortic graft + valve	12 (3)	2 (1)
ASD repair + valve	3 (0.7)	1 (0.4)
Need or surgery		
Elective	318 (76)	175 (77)
Urgent/emergent	99 (24)	52 (23)
Comorbidities		
CAD	278 (67)	164 (72)
Afib	81 (19)	42 (19)
AICD/PM	21 (5)	11 (5)
DM	137 (33)	89 (39)
PHTN	21 (5)	13 (6)
LD	27 (7)	18 (8)
KI	88 (21)	53 (23)
Active IE	6 (1)	2 (1)
IS	16 (4)	10 (4)

ICU: Intensive care unit; IQR: Interquartile range; BMI: Body mass index; CABG: Coronary artery bypass graft; ASD: Atrial septum defect; CAD: Coronary artery disease; Afib: Atrial fibrillation; AICD/PM: Automatic implantable cardioverter defibrillator/pacemaker; DM: Diabetes mellitus; PHTN: Pulmonary hypertension; LD: Liver disease; KI: Kidney injury; IE: Infective endocarditis; IS: Immunosuppressed.

0.14). Receipt of vasopressor bolus during the transfer was significantly associated with longer MV duration, ICU and hospital LOS ($P < 0.001$, for all). All variables with $\alpha \leq 0.1$ in univariate analysis were included in multivariate analysis. When adjusted in the multivariate analysis, CAD, DM and longer BT were significantly associated with the development of ICU hypotension (Table 4).

Mortality and secondary outcomes

Overall hospital mortality was not significantly associated with ICU hypotension (OR = 4.33; 95%CI: 0.94-20.02; $P = 0.073$); likely given relatively low overall mortality of 3% (Table 5). The female sex was significantly associated with longer ICU and hospital LOS, while longer BT and higher American Society of Anesthesiologists (ASA) physical status score were significantly associated with longer MV, ICU and hospital LOS. When adjusted for multiple covariates, no single variable was significantly

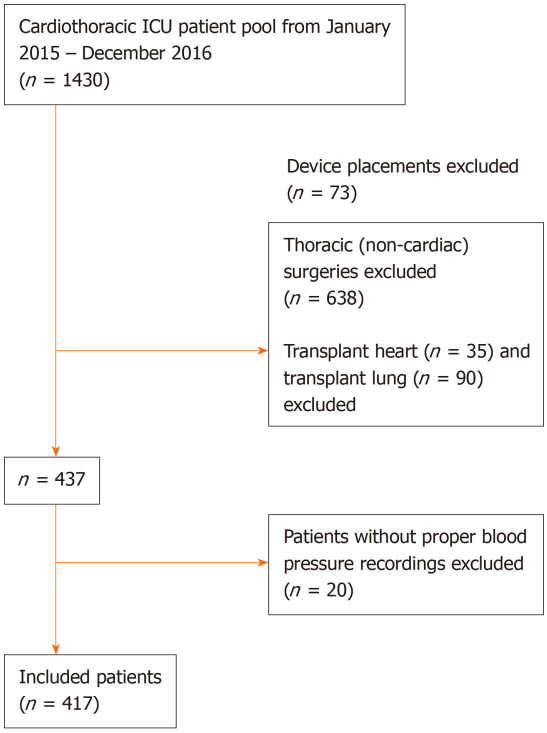

Figure 1 Schematic representation of the study population. ICU: Intensive care unit.

associated with the mortality. In order to avoid overfitting of the model, variables such as CCT (collinear with BT) and pulmonary hypertension (low frequency), were excluded.

DISCUSSION

In this retrospective study from a single academic center, we have demonstrated that hypotension in the initial 30 min upon ICU admission after cardiac surgery occurs more frequently than previously reported and this may be associated with adverse clinical outcomes. More than half of the patients received vasopressor boluses during the OR to ICU transfer, which has also been associated with adverse outcomes.

The results of our study have important implications for anesthesia and ICU practitioners. The frequency of hypotension in the first 30 min upon ICU arrival in our study was substantially higher (54%), relative to a European study which examined the hemodynamic status of cardiac surgical patients in the initial two-hour post-operative period (34%)[6]. It is likely that the frequency of hypotension could have been even higher in our study had we prolonged the observation period to two-hour period similar to the aforementioned study. Given that the patients with ICU hypotension may experience worse clinical outcomes, it is necessary to address potentially modifiable factors. In our cohort, significant unadjusted predictors for hypotension upon arrival to the ICU were elevated BMI, history of DM and CAD, all well-established risk factors for cardiovascular morbidity. After adjustments in the multivariate regression analysis, DM and longer cardiopulmonary bypass remained significantly associated with the development of ICU hypotension. Presence of DM has been previously associated with the higher cardiovascular morbidity, higher rates of pneumonia and sepsis, which may contribute to increased mortality, relative to non-diabetic patients[11-15]. It is important that both preoperative as well perioperative blood sugar control are maximized in order to reduce the hyperglycemia-related adverse outcomes[16-18]. Despite the fact that the significance of longer BT has been well documented to negatively affect post-operative rate of complications and mortality[19], our analysis (Table 5) does not show any significant difference between longer BT and mortality. It is plausible to expect that the future improvements in operative techniques and avoidance of cardiopulmonary bypass altogether would likely further reduce postoperative complications thus improving morbidity and mortality. During the time period of data collection, off-pump surgery was very infrequently done at our institution and this would not affect the results.

Previously, female sex was reported to be significantly associated with adverse

Table 2 Association of baseline characteristics with intensive care unit hypotension and mortality

Baseline characteristic	ICU hypotension, *n* = 227	No ICU hypotension, *n* = 190	*P* value	Alive, *n* = 405	Dead, *n* = 12	*P* value
Age, median (IQR)	67 (58, 74)	68 (59, 73)	0.73	67 (59, 73)	64 (59, 67)	0.42
Male sex, *n* (%)	172 (76)	133 (70)	0.22	299 (74)	6 (50)	0.0935
BMI, median (IQR)	29 (26, 33)	27 (25, 31)	0.01	28 (25, 32)	32 (27, 38)	0.039
CAD, *n* (%)	164 (72.2)	114 (60.0)	0.009	272 (67)	6 (50)	0.23
DM, *n* (%)	89 (39.2)	48 (25.3)	0.003	133 (33)	4 (33)	1.0
Afib, *n* (%)	42 (19)	39 (21)	0.62	78 (19)	3 (25)	0.71
AICD/PM, *n* (%)	11 (5)	10 (5)	1.00	20 (5)	1 (8)	0.47
PHTN, *n* (%)	13 (6)	8 (4)	0.51	18 (12)	3 (25)	0.018
IE, *n* (%)	2 (1)	4 (2)	0.42	6 (1)	0 (0)	1.0
LD, *n* (%)	18 (8)	9 (5)	0.23	27 (7)	0 (0)	1.0
KD, *n* (%)	53 (23)	35 (18)	0.23	86 (21)	2 (17)	0.78
IS, *n* (%)	10 (4)	6 (3)	0.61	16 (4)	0 (0)	1.0
Elective surgery, *n* (%)	175 (77)	143 (75)	0.73	309 (76)	9 (75)	1.0
ASA, *n* (%)			0.42			0.02
2	1 (0.5)	1 (0.4)		2 (0.5)	0 (0)	
3	94 (49)	94 (41)		186 (46)	2 (17)	
4	94 (49)	130 (57)		215 (53)	9 (75)	
5	1 (0.5)	2 (0.9)		2 (0.5)	1 (8)	
EF%, median (IQR)	60 (51, 64)	62 (54, 66)	0.29	60 (53, 65)	62 (53, 67)	0.62
BT, median (IQR)	117 (90, 150)	114 (85, 148)	0.10	115 (89, 148)	152 (108, 240)	0.0008
CCT, median (IQR)	81 (60, 105)	77 (53, 108)	0.10	80 (55, 105)	111 (59, 160)	0.018
Transfusion, n (%)	138 (61)	124 (65)	0.36	252 (62)	10 (83)	0.22
Pressors, *n* (%)	178 (78)	138 (73)	0.21	305 (75)	11 (92)	0.31
Bolus given, *n* (%)	125 (59.0)	87 (41.0)	0.06	203 (50)	9 (75)	0.14
Hb, median (IQR)	13 (12,14)	13 (12, 14)	0.79	13 (12, 14)	13 (10, 14)	0.48
Hct, median (IQR)	40 (35, 42)	40 (36, 42)	0.86	40 (36, 42)	40 (33, 44)	0.73
PLT, median (IQR)	203 (163, 248)	198 (159, 233)	0.18	201 (161, 243)	186 (155, 236)	0.69
Cre, median (IQR)	1.1 (0.9, 1.4)	1 (0.9, 1.2)	0.13	1 (0.9, 1.3)	1.1 (0.9, 1.9)	0.80
Ca, median (IQR)	9.3 (8.9, 9.6)	9.3 (8.9, 9.6)	0.78	9.3 (8.9, 9.6)	9.2 (8.6, 9.4)	0.49
Pre-op SBP, median (IQR)	125 (110, 139)	126 (110, 139)	0.69	126 (110, 139)	114 (98, 144)	0.18
Pre-op MAP, median (IQR)	84 (73, 94)	83 (74, 96)	0.89	84 (74, 95)	80 (49, 91)	0.066

ICU: Intensive care unit; IQR: Interquartile range; *n*: Number of patients; BMI: Body mass index; CAD: Coronary artery disease; DM: Diabetes mellitus; Afib: Arterial fibrillation; AICD/PM: Automatic implantable cardioverter defibrillator/pacemaker; PHTN: Pulmonary hypertension; IE: Infective endocarditis; LD: Liver disease; KD: Kidney disease; IS: Immunosuppressed; ASA: American Society of Anesthesiologists; EF: Ejection fraction; BT: Bypass time; CCT: Cross-clamp time; Hb: Hemoglobin; Hct: Hematocrit; PLT: Platelet; Cre: Creatinine; Ca: Calcium; pre-op: Pre-operation; SBP: Systolic blood pressure; MAP: Mean arterial pressure.

postoperative outcomes[20]. Females with the acute coronary syndrome resulting in cardiogenic shock, those with acute aortic dissection, ruptured abdominal aortic aneurysms, or those undergoing non-cardiac surgery, have been shown to have higher mortality rates compared to men[21-25]. Also, females with cerebral complications after cardiac surgery have shown to have a higher mortality than males[24,26]. In our study, females experienced significantly longer unadjusted ICU and hospital lengths of stay. Although the female sex was previously associated with the use of higher tidal volumes (relative to the height measurement) and more ventilator induced lung injury[27], there was no observed difference in duration of MV relative to the males in our cohort. There is a strong impetus for extubation of patients within 6 h of the cardiac surgery[28]. When adjusted for pertinent clinical variables and compared to men, females in our cohort were not more likely to die during the hospital stay.

The ASA physical status score subjectively assesses the patients' overall health prior to surgery. It has been shown that ASA score is associated with longer ICU and LOS, longer MV, and increased mortality[2,29,30]. In our study, ICU and LOS, as well as MV duration were significantly associated with ASA score, and there was a trend for higher hospital mortality with the rising ASA score, accordingly.

Based on the chart documentation, more than half of patients received boluses of short-acting vasopressors during the transfer from the OR to the ICU. The

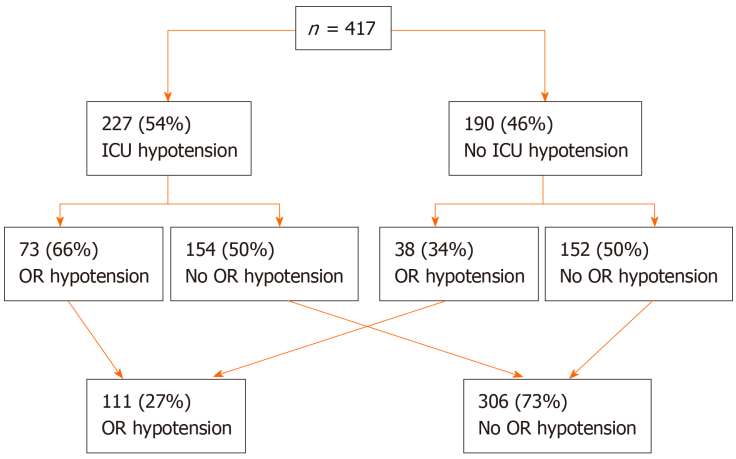

Figure 2 Intensive care unit and operating room hypotension frequency. ICU: Intensive care unit; OR: Operating room.

anesthesiology transport teams routinely carry syringes of resuscitative medications for any unanticipated needs that may occur during the transfer. It is possible that even more patients had received the bolus dosing without the subsequent chart documentation, although this is speculative. Why this may be important? Frequently, ICU receiving team may not be aware of use of vasopressor boluses during the transfer and the development of hypotension soon after the anesthesia drop-off is not anticipated, which leads to delayed and reactive treatment strategy that may be suboptimal. This is anecdotally termed "anesthesia drop-off syndrome" in the ICU, where soon after the transfer from the OR, the patients tend to develop hypotension that was not present at the arrival of the patient into the ICU and during the actual transfer of care from anesthesia to ICU team. As it has been previously suggested that hypotension is associated with adverse outcomes[11,13,31], it is important that any use of vasopressor bolus on transfer is readily communicated to the receiving ICU team, to enable anticipatory rather than reactive management of hypotension. For the same reasons, it may be more appropriate to up titrate the dose of ongoing vasopressor drip rather than to push additional IV bolus, as such bolus dosing may not be obvious to the receiving team. This is currently subject of qualitative improvement and patient safety initiatives spanning both anesthesiology and ICU providers at our institution, as the current process of care needs to be improved.

We have abstracted a vast amount of clinical information on all patients, including vital signs, complete blood counts, pertinent hemodynamic variables such as preoperative and intraoperative echocardiography (systolic and diastolic function, valvular function), transfusion of blood products and cell saver, administration of crystalloid and colloid solutions, CCT, estimated blood loss and development of other OR complications, among others. It is interesting that none of these variables were significant adjusted risk predictors by itself for developing hypotension upon ICU arrival. This implies that the perioperative management of cardiac surgery patients is complex and of a very dynamic nature where the multitude of factors play pertinent roles.

The main study limitation lies in its retrospective design. We relied on abstraction of data from the electronic medical records and at best our data is as good as the chart documentation itself. Relative to this, there might have been time delays between the exact occurrence of the event and the time it was documented in the chart. While this delay may have not been substantial during the intraoperative period, the retrospective charting of the medications administered during the actual patient transfer to the ICU may have been affected, including possibility for the lack of documentation, altogether. This may possibly in part explain why the substantial number of patients, who were not recorded to be hypotensive in the OR immediately prior to the transfer to the ICU, were documented to have received boluses of short-acting vasopressor medications during the transfer.

The study was done at the single academic medical center and since we excluded the patients who underwent transplantation surgery, these factors limit the generalizability of our findings to the certain extent. There was a relatively low mortality and therefore small number of patients who died predisposed multivariate model to overfitting and may not be completely reliable. At our institution, there are no established or preferred teams of certain surgeons and anesthesiologist. All surgeons work with all anesthesiologists depending only on the scheduling.

Table 3 Unadjusted association of intensive care unit hypotension with clinical outcomes

Item	ICU hypotension	No ICU hypotension	*P* value
Hosp. LOS, median (IQR)	7 (5, 10)	7 (5, 9)	0.49
ICU LOS, median (IQR)	2 (1, 4)	2 (1, 3)	0.21
MV hours, median (IQR)	5 (3, 15)	4 (3, 6)	< 0.001
Hosp. mortality, *n* (%)	10 (4.4)	2 (1.1)	0.07

ICU: Intensive care unit; Hosp: Hospital; LOS: Length of stay; IQR: Interquartile range; MV: Mechanical ventilation.

Therefore, it is unlikely that individual surgeons or anesthesiologists could affect the results.

Nevertheless, despite the above limitations, the high proportion of patients who were hypotensive immediately upon transfer from the OR to the ICU dictates the need for novel strategies and protocol implementations to assure the safest transition of care between the anesthesiology and ICU teams, which in turn may improve overall patient outcomes.

In summary, we have demonstrated that the occurrence of hypotension in the initial 30 min upon OR to ICU transfer is frequent and substantially more so than previously reported. Our findings have important implications for the anesthesia and ICU care teams as the occurrence of hypotension have been associated with adverse clinical outcomes. Administration of any medications during the actual transfer of the patient from the OR to the ICU should be readily communicated to the receiving ICU team. It is suggested that there is a room for improvement in the OR to ICU hand off process and renewed strategies that assure smooth transition of care and patient's safety are needed.

Table 4 Multivariate analysis for intensive care unit hypotension

Item	ICU hypotension	
	OR; 95%CI	*P* value
BMI	1.02; 0.99-1.07	0.13
CAD	1.69; 1.09-2.62	0.018
DM	1.66; 1.06-2.61	0.025
BT	1.004; 1.0002-1.008	0.034
Bolus	1.2; 0.79-1.82	0.38

Cross clamp time excluded because of linear correlation with bypass time. ICU: Intensive care unit; OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; CAD: Coronary artery disease; DM: Diabetes mellitus; BT: Bypass time.

Table 5 Multivariate analysis for mortality

Item	Mortality	
	OR; 95%CI	*P* value
Sex	0.74; 0.06-7.99	0.80
BMI	0.93; 0.76-1.14	0.51
ICU hypotension	0.27; 0.03-2.74	0.27
Lowest MAP (pre-op)	0.96; 0.89-1.02	0.19
BT	1.01; 0.43-23.8	0.33
ASA	3.19; 0.79-1.82	0.26

Cross clamp time excluded because of linear correlation with bypass time; Pulmonary hypertension (low frequency) excluded to prevent overfitting). OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; ICU: Intensive care unit; MAP: Mean artery pressure; pre-op: Pre-operative; BT: Bypass time; ASA: American Society of Anesthesiologists.

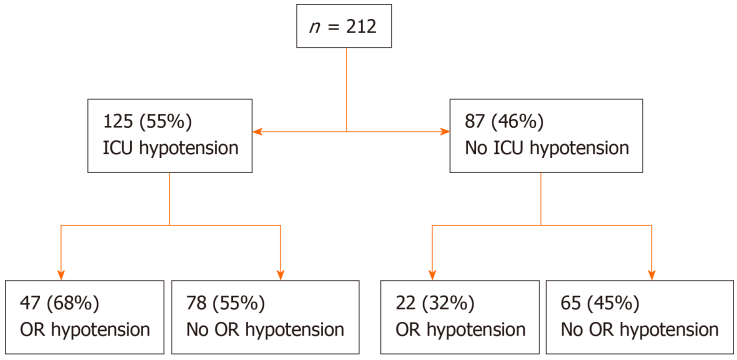

Figure 3 Number of patients receiving the vasopressor bolus on transfer. ICU: Intensive care unit; OR: Operating room.

ARTICLE HIGHLIGHTS

Research background

Perioperative hypotension is one of the most common complications after cardiac surgery and this may adversely affect clinical outcomes. However, data is limited in the literature regarding the actual prevalence of hypotension that develops shortly after the transfer of patients to the intensive care unit (ICU) after cardiac surgery. Hypotensive patients usually require administration of vasopressor boluses prior to or during the transfer from the operating room (OR) to the ICU as a temporizing measure. The hypotension and necessity for use of vasopressors have been previously associated with increased hospital length of stay as well as mortality, relative to the patients who maintained hemodynamic stability.

Research motivation

Given the proposed discrepancy between the clinical occurrence and limited data on rate of hypotension starting shortly after the anesthesia to ICU transfer, we aimed to evaluate its

prevalence and also how this may relate to the pertinent clinical outcomes.

Research objectives
We hypothesized that the occurrence of initial hypotension in the ICU is more frequent complication among post-cardiac surgery ICU patients than previously reported and that patients who experience this complication would have adverse clinical outcomes. We also aimed to better assess the association between the occurrence of initial hypotension in the ICU and the use of vasopressor bolus administered immediately prior to or during the transfer from the OR to the ICU.

Research methods
We conducted a retrospective study of adult patients undergoing cardiac surgery in a 2-year period. The primary independent variable was the development of hypotension within the first 30 min upon transfer from the OR ("ICU hypotension"). We abstracted demographic and baseline characteristics, comorbidities, and all pertinent clinical variables, as well as presence of hypotension in the OR ("OR hypotension"). A vasopressor bolus use was abstracted from the electronic chart documentation by the provider. All data were manually extracted from an electronic medical record. The anesthesia notes during the surgery were extracted partially from plotted diagrams and partially from nominal data.

Research results
We have demonstrated that hypotension in the initial 30 min upon ICU admission after adult cardiac surgery occurs more frequently than previously reported and this may be associated with adverse clinical outcomes. The results of our study have important implications for anesthesia and ICU practitioners. Given that the patients with ICU hypotension may experience worse clinical outcomes, it is necessary to address potentially modifiable factors. More than half of patients received boluses of short-acting vasopressors during the transfer from the OR to the ICU. Why this may be important? Frequently, ICU receiving team may not be aware of use of vasopressor boluses during the transfer and the development of hypotension soon after the anesthesia drop-off is not anticipated, which leads to delayed and reactive treatment strategy that may be suboptimal. This is currently subject of qualitative improvement and patient safety initiatives spanning both anesthesiology and ICU providers at our institution, as the current process of care needs to be improved. The main study limitation lies in its retrospective design. We relied on abstraction of data from the electronic medical records. The study was done at the single academic medical center and since we excluded the patients who underwent transplantation surgery, these factors limit the generalizability of our findings to the certain extent. Nevertheless, despite the above limitations, the high proportion of patients who were hypotensive immediately upon transfer from the OR to the ICU dictates the need for novel strategies and protocol implementations to assure the safest transition of care between the anesthesiology and ICU teams, which in turn may improve overall patient outcomes.

Research conclusions
We have demonstrated that the occurrence of hypotension in the initial 30 min upon OR to ICU transfer is frequent and substantially more so than previously reported. Our findings have important implications for the anesthesia and ICU care teams as the occurrence of hypotension have been associated with adverse clinical outcomes. Administration of any medications during the actual transfer of the patient from the OR to the ICU should be readily communicated to the receiving ICU team.

Research perspectives
It is suggested that there is a room for improvement in the OR to ICU hand off process and renewed strategies that assure smooth transition of care and patient's safety are needed.

REFERENCES

1 **Barbour CM**, Little DM. Postoperative hypotension. *J Am Med Assoc* 1957; **165**: 1529-1532 [PMID: 13475055 DOI: 10.1001/jama.1957.02980300009003]
2 **Brovman EY**, Gabriel RA, Lekowski RW, Dutton RP, Urman RD. Rate of Major Anesthetic-Related Outcomes in the Intraoperative and Immediate Postoperative Period After Cardiac Surgery. *J Cardiothorac Vasc Anesth* 2016; **30**: 338-344 [PMID: 26708695 DOI: 10.1053/j.jvca.2015.08.006]
3 **Hori D**, Ono M, Rappold TE, Conte JV, Shah AS, Cameron DE, Adachi H, Everett AD, Hogue CW. Hypotension After Cardiac Operations Based on Autoregulation Monitoring Leads to Brain Cellular Injury. *Ann Thorac Surg* 2015; **100**: 487-493 [PMID: 26089226 DOI: 10.1016/j.athoracsur.2015.03.036]
4 **Roock SD**, Mesana TG, and Sun L. "Abstract 13021: Impact of Preoperative Risk on the Association Between Hypotension and Mortality After Cardiac Surgery". *Circulation* 2019; **140**: A13021-A13021 [DOI: 10.1161/circ.140.suppl_1.13021]
5 **Sun LY**, Chung AM, Farkouh ME, van Diepen S, Weinberger J, Bourke M, Ruel M. Defining an Intraoperative Hypotension Threshold in Association with Stroke in Cardiac Surgery. *Anesthesiology* 2018; **129**: 440-447 [PMID: 29889106 DOI: 10.1097/ALN.0000000000002298]
6 **Currey J**, Botti M. The haemodynamic status of cardiac surgical patients in the initial 2-h recovery period. *Eur J Cardiovasc Nurs* 2005; **4**: 207-214 [PMID: 15935734 DOI: 10.1016/j.ejcnurse.2005.03.007]
7 **Magruder JT**, Dungan SP, Grimm JC, Harness HL, Wierschke C, Castillejo S, Barodka V, Katz N, Shah AS, Whitman GJ. Nadir Oxygen Delivery on Bypass and Hypotension Increase Acute Kidney Injury Risk After Cardiac Operations. *Ann Thorac Surg* 2015; **100**: 1697-1703 [PMID: 26271583 DOI: 10.1016/j.athoracsur.2015.05.059]

8 **Rady MY**, Ryan T, Starr NJ. Perioperative determinants of morbidity and mortality in elderly patients undergoing cardiac surgery. *Crit Care Med* 1998; **26**: 225-235 [PMID: 9468158 DOI: 10.1097/00003246-199802000-00016]

9 **Weis F**, Kilger E, Beiras-Fernandez A, Nassau K, Reuter D, Goetz A, Lamm P, Reindl L, Briegel J. Association between vasopressor dependence and early outcome in patients after cardiac surgery. *Anaesthesia* 2006; **61**: 938-942 [PMID: 16978306 DOI: 10.1111/j.1365-2044.2006.04779.x]

10 **Bijker JB**, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. *Anesthesiology* 2007; **107**: 213-220 [PMID: 17667564 DOI: 10.1097/01.anes.0000270724.40897.8e]

11 **Bannier K**, Lichtenauer M, Franz M, Fritzenwanger M, Kabisch B, Figulla HR, Pfeifer R, Jung C. Impact of diabetes mellitus and its complications: survival and quality-of-life in critically ill patients. *J Diabetes Complications* 2015; **29**: 1130-1135 [PMID: 26361811 DOI: 10.1016/j.jdiacomp.2015.08.010]

12 **Gadboys HL**, Wisoff G, Litwak RS. Surgical treatment of complete heart block. An analysis of 36 cases. *JAMA* 1964; **189**: 97-102 [PMID: 14149997 DOI: 10.1001/jama.1964.03070020025005]

13 **Kannel WB**, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. *Diabetes Care* 1979; **2**: 120-126 [PMID: 520114 DOI: 10.2337/diacare.2.2.120]

14 **Ouattara A**, Lecomte P, Le Manach Y, Landi M, Jacqueminet S, Platonov I, Bonnet N, Riou B, Coriat P. Poor intraoperative blood glucose control is associated with a worsened hospital outcome after cardiac surgery in diabetic patients. *Anesthesiology* 2005; **103**: 687-694 [PMID: 16192760 DOI: 10.1097/00000542-200510000-00006]

15 **Haines D**, Miranda HG, Flynn BC. The Role of Hemoglobin A1c as a Biomarker and Risk Assessment Tool in Patients Undergoing Non-cardiac and Cardiac Surgical Procedures. *J Cardiothorac Vasc Anesth* 2018; **32**: 488-494 [PMID: 29199050 DOI: 10.1053/j.jvca.2017.05.047]

16 **Doenst T**, Wijeysundera D, Karkouti K, Zechner C, Maganti M, Rao V, Borger MA. Hyperglycemia during cardiopulmonary bypass is an independent risk factor for mortality in patients undergoing cardiac surgery. *J Thorac Cardiovasc Surg* 2005; **130**: 1144 [PMID: 16214532 DOI: 10.1016/j.jtcvs.2005.05.049]

17 **Kotagal M**, Symons RG, Hirsch IB, Umpierrez GE, Dellinger EP, Farrokhi ET, Flum DR; SCOAP-CERTAIN Collaborative. Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes. *Ann Surg* 2015; **261**: 97-103 [PMID: 25133932 DOI: 10.1097/SLA.0000000000000688]

18 **Robich MP**, Iribarne A, Leavitt BJ, Malenka DJ, Quinn RD, Olmstead EM, Ross CS, Sawyer DB, Klemperer JD, Clough RA, Kramer RS, Baribeau YR, Sardella GL, DiScipio AW; Northern New England Cardiovascular Disease Study Group. Intensity of Glycemic Control Affects Long-Term Survival After Coronary Artery Bypass Graft Surgery. *Ann Thorac Surg* 2019; **107**: 477-484 [PMID: 30273572 DOI: 10.1016/j.athoracsur.2018.07.078]

19 **Shultz B**, Timek T, Davis AT, Heiser J, Murphy E, Willekes C, Hooker R. Outcomes in patients undergoing complex cardiac repairs with cross clamp times over 300 minutes. *J Cardiothorac Surg* 2016; **11**: 105 [PMID: 27406136 DOI: 10.1186/s13019-016-0501-4]

20 **Hassan A**, Chiasson M, Buth K, Hirsch G. Women have worse long-term outcomes after coronary artery bypass grafting than men. *Can J Cardiol* 2005; **21**: 757-762 [PMID: 16082435]

21 **Alonso-Pérez M**, Segura RJ, Sánchez J, Sicard G, Barreiro A, García M, Díaz P, Barral X, Cairols MA, Hernández E, Moreira A, Bonamigo TP, Llagostera S, Matas M, Allegue N, Krämer AH, Mertens R, Coruña A. Factors increasing the mortality rate for patients with ruptured abdominal aortic aneurysms. *Ann Vasc Surg* 2001; **15**: 601-607 [PMID: 11769139 DOI: 10.1007/s100160010115]

22 **Harris LM**, Faggioli GL, Fiedler R, Curl GR, Ricotta JJ. Ruptured abdominal aortic aneurysms: factors affecting mortality rates. *J Vasc Surg* 1991; **14**: 812-818; discussion 819-820 [PMID: 1960812 DOI: 10.1067/mva.1991.33494]

23 **Kamiński KA**, Tycińska AM, Stepek T, Szpakowicz A, Olędzka E, Dobrzycki S, Musiał WJ. Natural history and risk factors of long-term mortality in acute coronary syndrome patients with cardiogenic shock. *Adv Med Sci* 2014; **59**: 156-160 [PMID: 25323750 DOI: 10.1016/j.advms.2013.12.003]

24 **Nienaber CA**, Fattori R, Mehta RH, Richartz BM, Evangelista A, Petzsch M, Cooper JV, Januzzi JL, Ince H, Sechtem U, Bossone E, Fang J, Smith DE, Isselbacher EM, Pape LA, Eagle KA; International Registry of Acute Aortic Dissection. Gender-related differences in acute aortic dissection. *Circulation* 2004; **109**: 3014-3021 [PMID: 15197151 DOI: 10.1161/01.CIR.0000130644.78677.2C]

25 **Xu L**, Yu C, Jiang J, Zheng H, Yao S, Pei L, Sun L, Xue F, Huang Y. Major adverse cardiac events in elderly patients with coronary artery disease undergoing noncardiac surgery: A multicenter prospective study in China. *Arch Gerontol Geriatr* 2015; **61**: 503-509 [PMID: 26272285 DOI: 10.1016/j.archger.2015.07.006]

26 **Ridderstolpe L**, Ahlgren E, Gill H, Rutberg H. Risk factor analysis of early and delayed cerebral complications after cardiac surgery. *J Cardiothorac Vasc Anesth* 2002; **16**: 278-285 [PMID: 12073196 DOI: 10.1053/jcan.2002.124133]

27 **Gajic O**, Dara SI, Mendez JL, Adesanya AO, Festic E, Caples SM, Rana R, St Sauver JL, Lymp JF, Afessa B, Hubmayr RD. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med* 2004; **32**: 1817-1824 [PMID: 15343007 DOI: 10.1097/01.ccm.0000133019.52531.30]

28 **Kotfis K**, Szylińska A, Listewnik M, Lechowicz K, Kosiorowska M, Drożdżal S, Brykczyński M, Rotter I, Żukowski M. Balancing intubation time with postoperative risk in cardiac surgery patients - a retrospective cohort analysis. *Ther Clin Risk Manag* 2018; **14**: 2203-2212 [PMID: 30464493 DOI: 10.2147/TCRM.S182333]

29 **Lupei MI**, Chipman JG, Beilman GJ, Oancea SC, Konia MR. The association between ASA status and other risk stratification models on postoperative intensive care unit outcomes. *Anesth Analg* 2014; **118**: 989-994 [PMID: 24781569 DOI: 10.1213/ANE.0000000000000187]

30 **Collins TC**, Daley J, Henderson WH, Khuri SF. Risk factors for prolonged length of stay after major elective surgery. *Ann Surg* 1999; **230**: 251-259 [PMID: 10450740 DOI: 10.1097/00000658-199908000-00016]

31 **Brown DV**, O'Connor CJ. Hypotension after coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* 2000; **14**: 97-99 [PMID: 10698404 DOI: 10.1016/S1053-0770(00)90067-3]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2020 June 5; 9(2): 31-42

DOI: 10.5492/wjccm.v9.i2.31

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Observational Study

Critical care practice in India: Results of the intensive care unit need assessment survey (ININ2018)

Rahul Kashyap, Kirtivardhan Vashistha, Chetan Saini, Taru Dutt, Dileep Raman, Vikas Bansal, Harpreet Singh, Geeta Bhandari, Nagarajan Ramakrishnan, Harshit Seth, Divya Sharma, Premkumar Seshadri, Mradul Kumar Daga, Mohan Gurjar, Yash Javeri, Salim Surani, Joseph Varon, ININ-2018 Investigators Team

ORCID number: Rahul Kashyap (0000-0002-4383-3411); Kirtivardhan Vashistha (0000-0003-4945-1980); Chetan Saini (0000-0003-4117-6347); Taru Dutt (0000-0003-1705-3558); Dileep Raman (0000-0002-8313-4340); Vikas Bansal (0000-0001-6047-5559); Harpreet Singh (0000-0001-9507-5248); Geeta Bhandari (0000-0002-7976-8252); Nagarajan Ramakrishnan (0000-0001-5208-4013); Harshit Seth (0000-0003-4615-8017); Divya Sharma (0000-0003-3581-8446); Premkumar Seshadri (0000-0002-2203-6720); Mradul Kumar Daga (0000-0001-7774-7602); Mohan Gurjar (0000-0002-8489-0324); Yash Javeri (0000-0002-7384-3637); Salim Surani (0000-0001-7105-4266); Joseph Varon (0000-0002-7622-9974).

Author contributions: All listed authors provided intellectual contribution and made critical revisions of this paper; Kashyap R, Ramakrishnan N, Daga MK, Seshadri P and Javeri Y contributed to study conception and design; All co-authors contributed to data acquisition; Vashistha K, Saini C and Kashyap R contributed to data analysis; Surani S and Varon J contributed to data interpretation and critical edits; all authors approved the final version of the manuscript.

Institutional review board statement: This study was deemed eligible for category-2 Institutional Review Board exempt status from

Rahul Kashyap, Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN 55905, United States

Kirtivardhan Vashistha, Department of Infectious Disease, Mayo Clinic, Rochester, MN 55905, United States

Kirtivardhan Vashistha, Department of Internal Medicine, Allegheny General Hospital, Pittsburgh, PA 15212, United States

Chetan Saini, Department of Radiology, Mayo Clinic, Rochester, MN 55905, United States

Chetan Saini, Department of Medicine, Jacobi Medical Center/Albert Einstein College of Medicine, Bronx, NY 14061, United States

Taru Dutt, Department of Neurology, Mayo Clinic, Rochester, MN 55905, United States and Department of Psychiatry, Hennepin County Medical Center, Minneapolis, MN 55415, United States

Dileep Raman, Department of Medicine, Cloud Physician Healthcare, Bangalore 560038, India

Vikas Bansal, Department of Critical Care Medicine, Mayo Clinic, Rochester, MN 55905, United States

Harpreet Singh, Department of Internal Medicine, Maulana Azad Medical College & Associated Hospitals, New Delhi, Delhi 110002, India

Geeta Bhandari, Department of Anesthesiology, Government Medical College, Haldwani, Nainital 263129, India

Nagarajan Ramakrishnan, Department of Critical Care Medicine, Apollo Hospitals, Chennai 600006, India

Harshit Seth, Department of Hospitalist Medicine, Allegany Clinic, Allegany Health Network, Pittsburgh, PA 15222, United States

Divya Sharma, Premkumar Seshadri, Department of Medicine, MAAGF Healthcare, Chennai 600024, India

Mradul Kumar Daga, Department of Internal Medicine and Center for Occupational and Environment Health, Maulana Azad Medical College, New Delhi, Delhi 110002, India

Mohan Gurjar, Department of Critical Care Medicine, Sanjay Gandhi Postgraduate Institute of

Mayo Clinic IRB, Mayo Clinic, Rochester, MN, 55905, United States.

Informed consent statement: Informed consent was waived by IRB, as it being a survey and no human subject was involved.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

STROBE statement: We have read the Strobe statement and prepared checklist and the manuscript accordingly.

Manuscript source: Unsolicited manuscript

Received: December 7, 2019
Peer-review started: December 7, 2019
First decision: January 28, 2020
Revised: April 27, 2020
Accepted: May 12, 2020
Article in press: May 12, 2020
Published online: June 5, 2020

P-Reviewer: Kumar N, Weiss M
S-Editor: Ma YJ
L-Editor: A
E-Editor: Wu YXJ

Medical Sciences, Lucknow 226014, India

Yash Javeri, Department of Critical Care Medicine, Regency Super Speciality Hospital, Lucknow 208005, India

Yash Javeri, Nayati Healthcare, New Delhi, Delhi 110065, India

Salim Surani, Department of Pulmonary and Critical Care Medicine, Texas A&M University, College Station, TX 77843, United States

Joseph Varon, Department of Critical Care, United Memorial Medical Center, Houston, TX 77091, United States

Corresponding author: Rahul Kashyap, MBBS, MBA, Assistant Professor, Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States. kashyap.rahul@mayo.edu

Abstract

BACKGROUND

A diverse country like India may have variable intensive care units (ICUs) practices at state and city levels.

AIM

To gain insight into clinical services and processes of care in ICUs in India, this would help plan for potential educational and quality improvement interventions.

METHODS

The Indian ICU needs assessment research group of diverse-skilled individuals was formed. A pan- India survey "Indian National ICU Needs" assessment (ININ 2018-I) was designed on google forms and deployed from July 23rd-August 25th, 2018. The survey was sent to select distribution lists of ICU providers from all 29 states and 7 union territories (UTs). In addition to emails and phone calls, social medial applications-WhatsApp™, Facebook™ and LinkedIn™ were used to remind and motivate providers. By completing and submitting the survey, providers gave their consent for research purposes. This study was deemed eligible for category-2 Institutional Review Board exempt status.

RESULTS

There were total 134 adult/adult-pediatrics ICU responses from 24 (83% out of 29) states, and two (28% out of 7) UTs in 61 cities. They had median (IQR) 16 (10-25) beds and most, were mixed medical-surgical, 111(83%), with 108(81%) being adult-only ICUs. Representative responders were young, median (IQR), 38 (32-44) years age and majority, n = 108 (81%) were males. The consultants were, n = 101 (75%). A total of 77 (57%) reported to have 24 h in-house intensivist. A total of 68 (51%) ICUs reported to have either 2:1 or 2≥:1 patient:nurse ratio. More than 80% of the ICUs were open, and mixed type. Protocols followed regularly by the ICUs included sepsis care, ventilator- associated pneumonia (83% each); nutrition (82%), deep vein thrombosis prophylaxis (87%), stress ulcer prophylaxis (88%) and glycemic control (92%). Digital infrastructure was found to be poor, with only 46 % of the ICUs reporting high-speed internet availability.

CONCLUSION

In this large, national, semi-structured, need-assessment survey, the need for improved manpower including; in-house intensivists, and decreasing patient-to-nurse ratios was evident. Sepsis was the most common diagnosis and quality and research initiatives to decrease sepsis mortality and ICU length of stay could be prioritized. Additionally, subsequent surveys can focus on digital infrastructure for standardized care and efficient resource utilization and enhancing compliance with existing protocols.

Key words: Intensive care unit; Critical care; India; Survey; Intensive care unit survey; Intensive care unit needs

Core tip: Intensive care unit (ICU) practices are variable in a vast country like India. Most common admitting diagnosis for ICU is similar to Western reporting in literature. There is variable protocol penetration for processes of care in ICU.

Citation: Kashyap R, Vashistha K, Saini C, Dutt T, Raman D, Bansal V, Singh H, Bhandari G, Ramakrishnan N, Seth H, Sharma D, Seshadri P, Daga MK, Gurjar M, Javeri Y, Surani S, Varon J, ININ-2018 Investigators Team. Critical care practice in India: Results of the intensive care unit need assessment survey (ININ2018). *World J Crit Care Med* 2020; 9(2): 31-42
URL: https://www.wjgnet.com/2220-3141/full/v9/i2/31.htm
DOI: https://dx.doi.org/10.5492/wjccm.v9.i2.31

INTRODUCTION

Critical care practices vary worldwide and are a reflection of varying epidemiology and existing financial and human resources. Patient outcomes in these centers can vary dramatically due to the influence of interlinked, multiple factors[1].

A diverse country like India, may have variable intensive care units (ICUs) practices in various states, which can be due to differences in; hierarchical arrangements, allocation of resources, patient backgrounds, cultural and clinical practices, and goals or objectives of the caregivers[2]. Although it is imperative to have standardized care of practice to minimize variations and maximize the quality of care delivered to the patients, it is essential to paint a picture in the backdrop keeping in mind the epidemiological context, resource availability, and local practices[3]. In addition, it is crucial to identify and evaluate variables like prevalent clinical practices, protocols, a range of service, human resources and facilities available on a national level to bring forth a prototype which will help in quality control and unification of the care delivery. Studies have been done in developed countries[3,4], and a few more describe the practices in a multinational setting[5-7] but the information is scarce in an Indian setting[2].

Our study aimed to gain insight into clinical services, prevalent practices, processes of care and patient outcomes in ICUs across different regions of India. Studying and analyzing these patterns can potentially help prioritize quality improvement interventions, educate practicing physicians and, create a framework for further studies to fill in the knowledge gap, to further strategize best care practices and act as a paradigm for critical care delivery.

MATERIALS AND METHODS

This was a cross-sectional pan-India survey-based study. We created a multidisciplinary, diverse team of qualified individuals who constituted the "Indian ICU needs assessment research group".

A questionnaire was designed to assess the ICU clinical practices prevalent in the institution followed by the study of the demographics of the institution and the surveyor. Questions were asked regarding the ICU being closed or open, group and type of patients catered to, number of ICU beds, protocols followed in the ICU setting, top diagnoses of the admitted patients, and availability of critical care equipment and technology. Moreover, human resource demographics were explored through variables such as the presence of certified intensivists, residents/fellows, 24-h in-house staff intensivists, patient: Nurse ratio, age of the surveyor, gender, level of training, and years of experience. Outcome variables included average ICU length of stay, mechanical ventilation duration, ICU mortality, sepsis mortality and, mechanical ventilation patient mortality. The functionality of the survey was tested as a pilot among a random group of critical care physicians prior to implementation for internal validity. A sample of the survey is depicted in the E-supplement.

A database of intensivists was identified through critical care societies, social media, and personal networks. The team carried out the study through a survey from July 23rd to August 25th, 2018, through an anonymous questionnaire designed on a Google™ form online and distributed to the critical care providers in 29 states and 7 Union territories (UTs) of India (Figure 1). Various platforms like electronic mail (e-mail), social media applications such as WhatsApp™, Facebook™ and LinkedIn™,

were used for dispatching the form and to reach out to potential collaborators for reminder and motivation.

A convenient sample of 134 ICUs was collected through the survey, and the data collected is presented as mean, with standard deviation, or median with interquartile range. Pictorial and graphical representation of the relevant data was done.

For analysis purposes, we divided India into 6 zones (Figure 2), on the basis of administrative divisions mainly – North, South, West, East, Central, Northeast[8]. Descriptive statistical analysis was used.

By completing and submitting the survey, providers gave their consent to provide pertinent information for research purposes. This study was deemed eligible for category-2 Institutional Review Board exempt status.

RESULTS

Representation

Our analysis was based on total 134 adult/adult-pediatrics ICU responses. They represented 61 cities of 24 states, and two UTs of India. The response rate was 83% states and 28% of UTs. Region-wise sample distribution revealed that 39 (29%) of entries belonged to the Northern region, whereas South Indian cities contributed to 34 (25%) entries. Thirteen (10%) from the Central; 25 (19%) from West; while 18 (13%) entries belonged to East and North-East, contributed 5 (4%) of the total of 134 entries.

Demographics

A vast majority of responders in the survey were young adults, median (IQR), 38 (32-44) years age and predominantly, *n* = 108 (80%) were males, with a median clinical ICU experience of 8.5 (IQR, 4-14) years. Likewise, most of the responses came from consultants, *n* = 101 (75%), followed by residents (PGY-3 and above), *n* = 19 (14%). Most of them were working in mixed medico-surgical ICUs, *n* = 111(83%) in private academic hospitals, *n* = 50 (37%) with median (IQR) 16 (10-25) beds. Most of the responders were working in open type of ICU setup, 110 (82%), and only 24 (18%) of them in closed ICUs (Table 1 and Figure 3).

Clinical resources

Intensivist and the nurses played a major role in ICU patient care. Most responders (62%), had patient: nurse ratio of 2:1, and only (10%) responders were strictly abiding by 1:1 nursing care. Additionally, 37% of ICUs, which usually had 2:1 patient: nurse ratios, switched to 1:1 for complicated cases. Also, more than 2:1 patient: nurse's ratios were reported in 24% of ICUs. A total of 107 (80%) reported to have ICU staffed by certified intensivists and 77 (58%), had 24 h in-house intensivist coverage to take care of the patients. The majority of ICUs (*n* = 110, 82%) ICUs had residents/fellows/medical students rotating through or cover ICU along with staff intensivists (Table 2 and Figure 4).

Critical care clinical protocols

The majority of ICUs had glycemic control (92%) protocols, Advanced Cardiac Life Support (89%), deep vein thrombosis prophylaxis (87%), stress ulcer prophylaxis (87%), sepsis care (84%), ventilator-associated pneumonia (84%) and nutrition (83%) protocols. The least reported protocols included palliative care/end-of-life care (50%), delirium assessment and treatment (49%), early mobility (49%) and targeted temperature management after cardiac arrest (45%) (Table 3 and Figure 5).

Digital infrastructure

In spite, of 60 (46%) hi-speed internet availability the digital infrastructure was reported to be limited. Electronic medical records, *n* = 49 (37%), tele-ICU coverage, *n* = 28 (21%) and 2-way communication including webcam, *n* = 21 (16%) were reported (Table 4).

Admitting diagnosis

The self-reported top admitting diagnosis in our survey study was sepsis, closely followed by respiratory failure (Table 5).

Outcomes

The self-reported average ICU mortality (*n* = 95) was *median* 18% (IQR 11-30); ICU length of stay (*n* = 112) was 3.5 (4-6) d; mechanical ventilation (MV) duration (*n* = 98) was *median* 4 (3-5) d; MV patient mortality (*n* = 77) was 25% (15%-40%) and sepsis mortality (*n* = 75) was 30% (20%-40%).

Figure 1 Distribution of participating intensive care unit's over India's map[17].

DISCUSSION

Our survey describes some of the critical care practices in a convenient sample of 134 Indian ICUs, and for a better visualization we aimed to cover the whole country, and data was collected from majority of states and some union territories. We found substantial variation in the representation, with minimal participation being observed from North-East region. The majority of the responders of the survey were young adult men, practicing as intensivists, supporting the notion that the country has been training more individuals in critical care, and expanding its health infrastructure.

The Indian subcontinent has variations abound, and each geographical region in the country blending with its own cultural and regional diversity constructs a polychromatic picture. It is only natural for the country to have diversified patient care practices. While being appreciative of the uniqueness this land offers, it is imperative to be vigilant for any disparities which may compromise the delivery of quality and standardized patient care.

Most of the ICUs we surveyed were mixed (medical-surgical) in nature, open in type with an average number of beds of less than 20 per hospital. More than half of them were privately owned, academic-nonacademic institutions. Likewise, elaborating clinical resource parameters, such as a ≤ 2:1 patient-nurse ratio[9], 24-h certified intensivists, and certified intensivists, are associated with better outcomes in intensive care. The majority of Indian ICUs reported having 1 nurse for two or more patients with only few reporting 1:1 patient-nurse ratio. The new finding is that the majority of the ICUs reported having a certified intensivist, and more than half of them had 24 h-in house intensivist coverage.

In a survey-based study done in India covering 400 ICUs, similar results were reported with average age of responders being 30-40 years, number of ICU beds 10-30, and the majority of the ICUs were open type and mixed in nature[2].

The top admitting diagnosis in our study was sepsis, which was reported across an over whelming majority of all the ICUs closely followed by respiratory failure. This follows global trends. For example, an observational study, collecting data from 10096 patients across different countries, observed the most common diagnosis on admission to be sepsis[10].

Recent reports suggest that standardized protocols and best practice guidelines in the treatment of the critically ill patients in the ICU are associated with more favorable outcomes and decreased ICU-related morbidity and mortality. In our survey, self-reported data suggested that the majority of the ICUs across India followed the glycemic control, Advanced Cardiac Life support, deep vein thrombosis prophylaxis, stress ulcer prophylaxis, severe sepsis, ventilator Associated pneumonia bundle, and nutrition protocols. Some of the protocols that still require widespread penetration and awareness in India included palliative care/end-of-life, delirium, early mobility and targeted temperature management after cardiac arrest.

With the advent of digital revolution in India, we also explored the depth of digital coverage in the ICU. Not aligning with the rapid growth observed in other sectors,

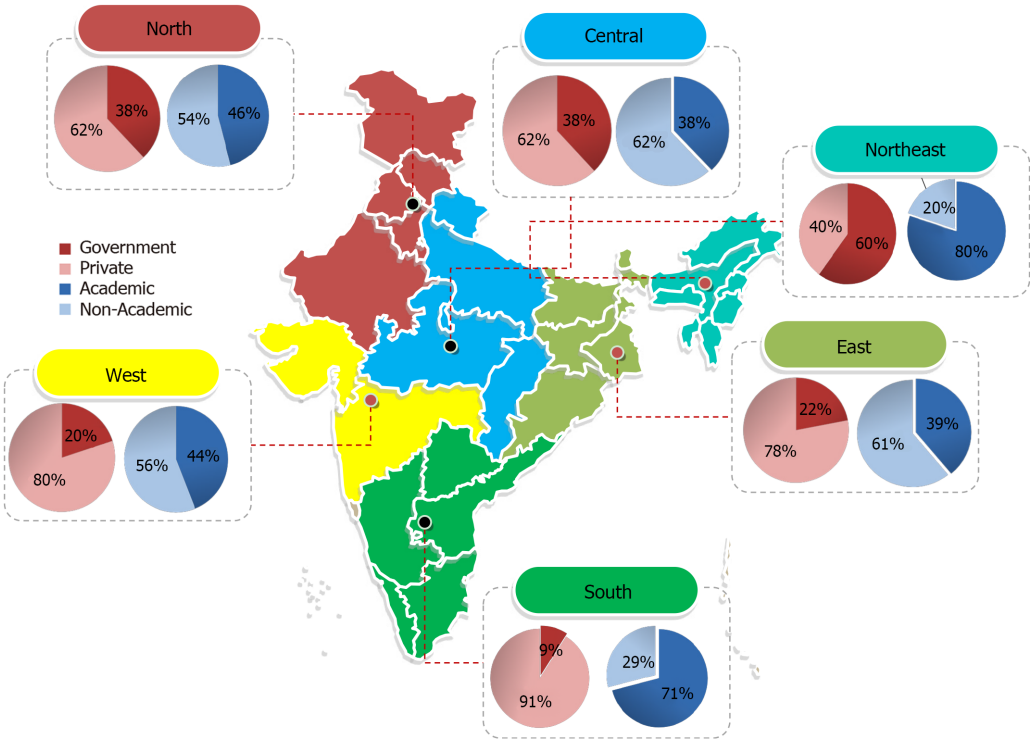

Figure 2 Participating intensive care unit's distribution by administrative divisions of India – North, South, West, East, Central, Northeast- with type of hospital setting.

less than half of the ICUs reported having high-speed internet with even lesser having electronic medical records, tele-ICU coverage and 2-way communication. A survey of ICUs in medium to low income countries documented an average number of beds being around 10 per ICU, almost 70% of the ICUs were staffed with certified intensivists and 69% of the hospitals had a reliable internet access[7]. In a systematic review done 18 years ago in an attempt to identify physician staffing patterns and clinical outcomes in critically ill patients, the ICU mortality rates ranged from 6%-74% in low intensity staffing and 1%-57% in high intensity staffing ICUs[11]. Outcome data in our study was well within the observed range, reflecting that the majority of the ICUs across the country are adhering to the accepted standard of care, although the self-reported outcomes decrease the validity of these results.

In a descriptive study in the United States of ICUs, the average ICU size was 11.7 ± 7.8 beds per unit, and majority of these hospitals had more than one ICU, followed standard of care protocols, had better patient care delivery, as well as better outcomes, as compared to studies done in low and middle income countries[2,12,13].

Our study has several limitations. First, we had no follow up of initial non-responders. We had a limited sample size, and we used a survey that had not been previously validated in the literature. Other limitations included the documentation of self-reported outcomes reporting, which is similar to previously reported survey-based study from one state in India[14,15]. Also, our study had a limited ability from the surveyor's side to ensure correct data entry and eliminate bias. For example, the overall penetration of tele-ICUs systems and EMRs in India is extremely low; but the reported fraction of tele-ICU penetration in our study may be higher due to selection bias. However, the strength of this survey is that the ICU data was retrieved from diverse geographical regions, which increase the external validity of the study. In addition, we were appreciated at Society of Critical Care Medicine 2019 conference abstract presentation[16] about the fact that the functionality of the survey was tested as a pilot among a random group of critical care physicians prior to implementation, which adds to the internal validity.

Understanding the epidemiology of the Indian subcontinent is incredibly complex, due to inherent variability and lack of required infrastructure to carry out such large-scale studies. At best, these trends can be used as building blocks to identify the gaps in the understructure, and identify areas to focus on, for improved financial and human resource investments.

In a large nation, semi-structured need assessment survey, the need for improved manpower including; in-house intensivists and decreasing patient-to-nurse ratios are evident. Quality and research initiatives to decrease sepsis mortality and ICU length

Table 1 Demographic variables

Demographic variables	Responses in % (*n* = 134)
Age (yr)	
30-40	41
40-50	30.6
20-30	17.2
> 50	11.2
Gender	
Male	80.2
Female	19.4
ICU experience (yr)	
< 10	61.9
11-20	28.4
20-30	8.2
> 30	1.5
Designation	
Consultant staff	75.4
Resident- PGY-3 and above	14.1
Resident- PGY-1	6.7
Resident- PGY-2	3.7
Intensive care unit specialty wise distribution	
Mixed medical-surgical	82.8
Medical	8.2
Others	6.7
Surgical	2.2
Institution type	
Private/academic	37.3
Private/non-academic	36.5
Government/academic	14.2
Government/non-academic	11.9
Bed strength	
11-20	36.6
< 10	26.9
21-30	22.4
> 30	14.2
ICU type	
Open	82.1
Closed	17.9

ICU: Intensive care unit.

of stay can be prioritized. Our new theory would be that subsequent surveys can focus on digital infrastructure for standardized care and scarce resources utilization and enhancing the compliance of existing protocols.

Table 2 Clinical resource parameters

Clinical resource parameters	Responses in % (*n* = 134)
Patient:nurse ratio	
Usually 2:1 (for complicated patients 1:1) (*n* = 49)	36.6
2:1 (*n* = 34)	25.4
> 2:1 (*n* = 32)	23.9
1:1 (*n* = 13)	9.7
No fixed patient:nurse (*n* = 6)	4.5
24 h in-house intensivist (*n* = 77)	57.5
Certified intensivist (*n* = 107)	79.9
Residents/fellows/medical students rotate through or cover ICU along with staff intensivists (*n* = 110)	82.1

ICU: Intensive care unit.

Table 3 Critical care protocols self-reporting

Critical care protocols self-reporting					
High (%)		**Medium (%)**		**Low (%)**	
Glucose control	91.8	Daily interruption of sedation	71.6	Palliative care/end of life	50.0
Advanced cardiac life support	88.8	Acute coronary syndrome	68.7	Delirium	48.5
DVT prophylaxis	87.3	Acute lung injury	62.7	Early mobility	48.5
Stress ulcer prophylaxis	87.3	Transfusion restriction	62	Hypothermia after cardiac arrest	44.8
Severe sepsis	83.5				
VAP bundle	83.5				
Nutrition	82.8				

DVT: Deep vein thrombosis.

Table 4 Digital demographics

Digital demographics	Responses in % (*n* = 134)
High speed internet	46
Electronic medical records	37
Tele-ICU Coverage	21
2 – way communication (*e.g.*, webcam)	16

ICU: Intensive care unit.

Table 5 Common diagnoses

Common diagnoses (Dx)	No.	% of ICU
Most common Dx - septic shock	116	86.57
Respiratory failure	108	80.6
Heart failure	58	43.28
Trauma	57	42.54
Post Op	59	44.03
COPD exacerbation	72	53.73
Electrolyte imbalance	39	29.1
Epilepsy or seizure	21	15.67
Renal failure	72	53.73
Hypotension	37	27.61

Poisoning/substance abuse	34	25.37

ICU: Intensive care unit.

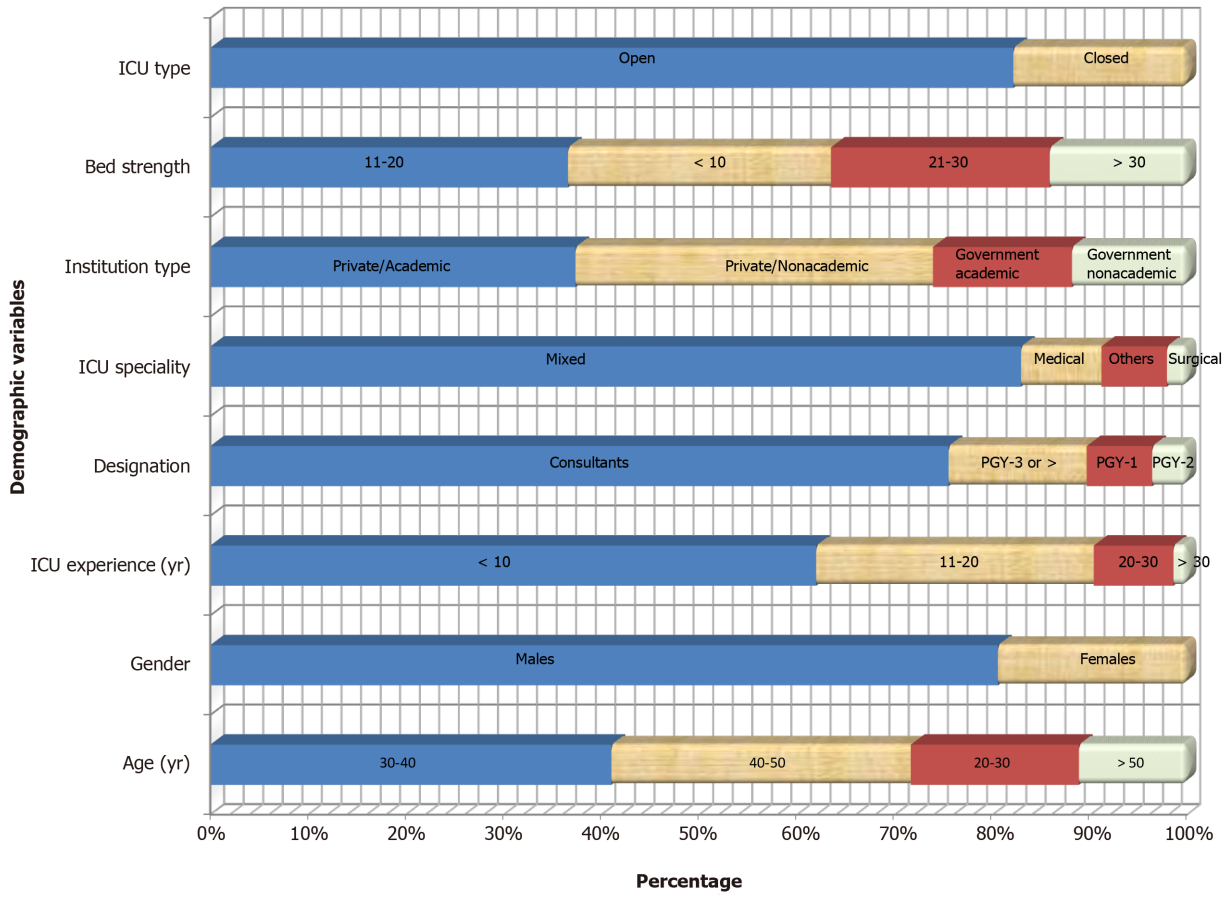

Figure 3 Intensive care unit demographics variables. ICU: Intensive care unit.

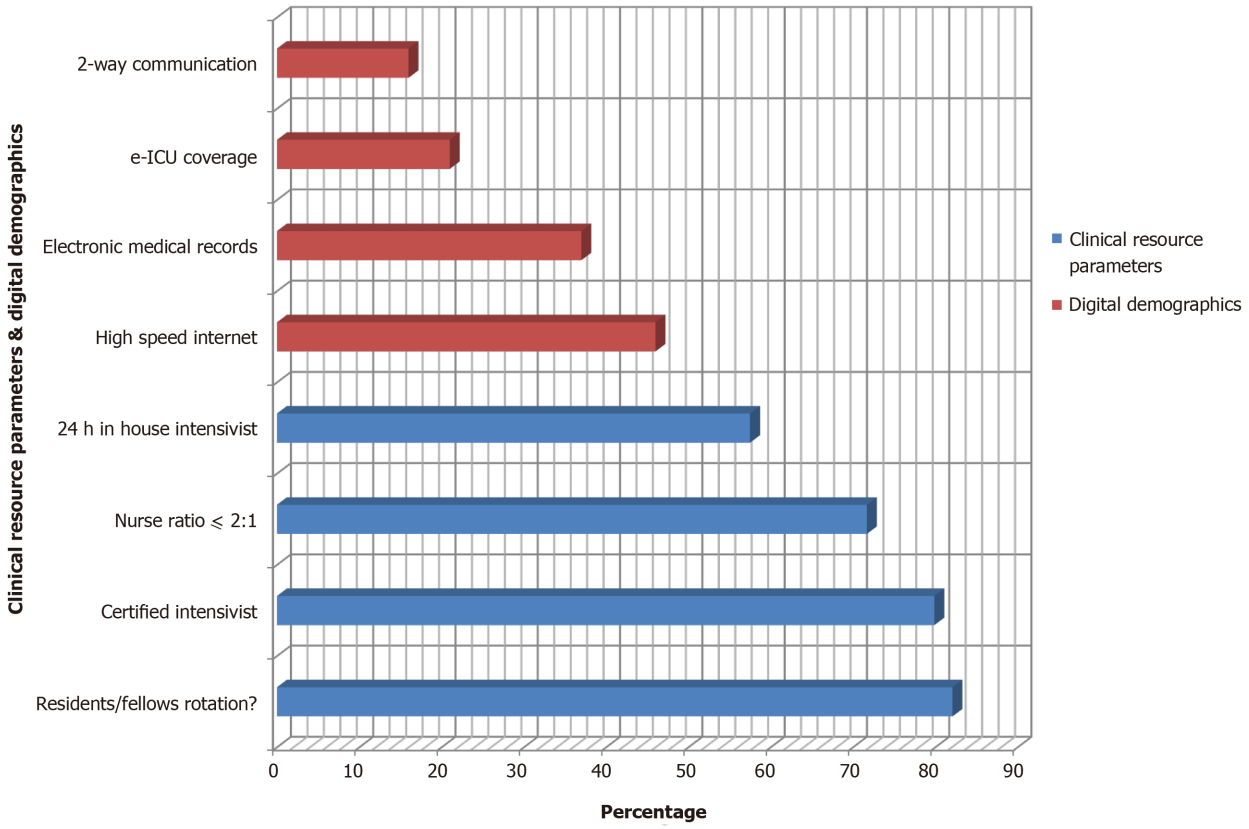

Figure 4 Intensive care unit clinical resource parameters and digital demographics.

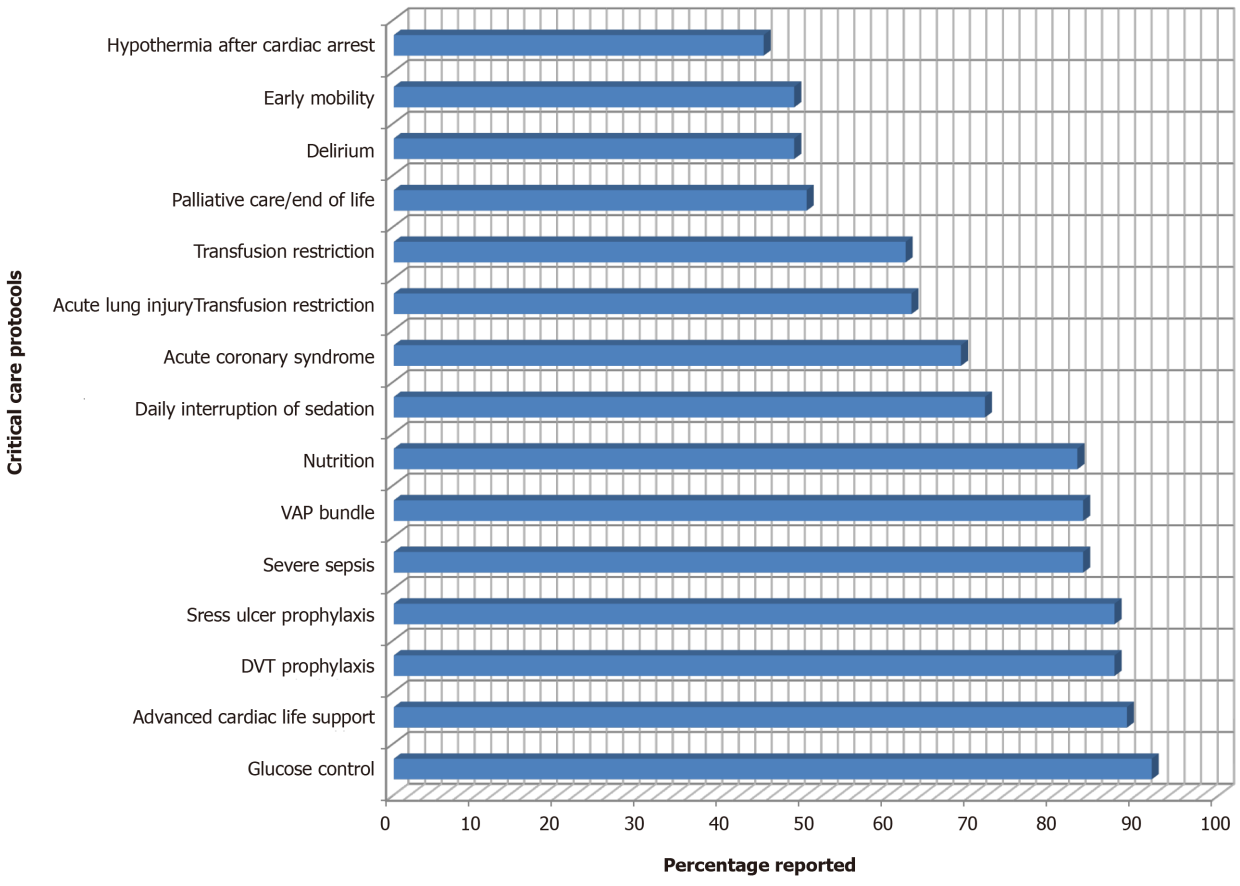

Figure 5 Intensive care unit critical care protocols.

ARTICLE HIGHLIGHTS

Research background

With the modernization of medicine and technology, the population is living longer. The patients presenting in hospital have several co-morbid factors and are critically ill on many instances. The developed countries have come with several protocol and best practices, based on the scientific facts and expert guideline. This has shown to save lives and improve the outcomes. When it comes to developing countries, though progress has been made but not much data or information is available.

Research motivation

There is not much data out there regarding standard of practice, variations in practice, clinical services available in the different region of intensive care unit (ICU). We believe that having that knowledge will help in decreasing the variation and improve henceforth help in improving the patient care.

Research objectives

Study was designed to understand the processes, adherence to the guidelines and clinical services available in ICU in different part of India.

Research methods

This study was cross-sectional pan-India based survey.

Research results

Responses were received from 134 adult/pediatric ICU were received. More than 80% of their ICU was either open or transitional. Digital infra-structure and technology was found to be marginal. More than 80% of them were utilizing sepsis care, ventilator-associated pneumonia bundle, deep venous thrombosis prophylaxis, stress ulcer prophylaxis and glycemic control. They have lower nurse to patient ratio. They also have fewer critical care specialist.

Research conclusions

There is definitely need for improvement in the digital infra-structure, nurse to patient ratio, critical care physician availability.

Research perspectives

Improving the practice gaps can help in improving the patient care, decreasing the hospital and ICU length of stay, decrease in mortality, and improvement in patient outcome.

REFERENCES

1 **Sakr Y**, Moreira CL, Rhodes A, Ferguson ND, Kleinpell R, Pickkers P, Kuiper MA, Lipman J, Vincent JL; Extended Prevalence of Infection in Intensive Care Study Investigators. The impact of hospital and ICU organizational factors on outcome in critically ill patients: results from the Extended Prevalence of Infection in Intensive Care study. *Crit Care Med* 2015; **43**: 519-526 [PMID: 25479111 DOI: 10.1097/CCM.0000000000000754]

2 **Kartik M**, Gopal PBN, Amte R. Quality Indicators Compliance Survey in Indian Intensive Care Units. *Indian J Crit Care Med* 2017; **21**: 187-191 [PMID: 28515601 DOI: 10.4103/ijccm.IJCCM_164_15]

3 **Checkley W**, Martin GS, Brown SM, Chang SY, Dabbagh O, Fremont RD, Girard TD, Rice TW, Howell MD, Johnson SB, O'Brien J, Park PK, Pastores SM, Patil NT, Pietropaoli AP, Putman M, Rotello L, Siner J, Sajid S, Murphy DJ, Sevransky JE; United States Critical Illness and Injury Trials Group Critical Illness Outcomes Study Investigators. Structure, process, and annual ICU mortality across 69 centers: United States Critical Illness and Injury Trials Group Critical Illness Outcomes Study. *Crit Care Med* 2014; **42**: 344-356 [PMID: 24145833 DOI: 10.1097/CCM.0b013e3182a275d7]

4 **Fowler RA**, Abdelmalik P, Wood G, Foster D, Gibney N, Bandrauk N, Turgeon AF, Lamontagne F, Kumar A, Zarychanski R, Green R, Bagshaw SM, Stelfox HT, Foster R, Dodek P, Shaw S, Granton J, Lawless B, Hill A, Rose L, Adhikari NK, Scales DC, Cook DJ, Marshall JC, Martin C, Jouvet P; Canadian Critical Care Trials Group; Canadian ICU Capacity Group. Critical care capacity in Canada: results of a national cross-sectional study. *Crit Care* 2015; **19**: 133 [PMID: 25888116 DOI: 10.1186/s13054-015-0852-6]

5 **Chittawatanarat K**, Sataworn D, Thongchai C; Thai Society of Critical Care Medicine Study Group. Effects of ICU characters, human resources and workload to outcome indicators in Thai ICUs: the results of ICU-RESOURCE I study. *J Med Assoc Thai* 2014; **97** Suppl 1: S22-S30 [PMID: 24855839]

6 **Murthy S**, Leligdowicz A, Adhikari NK. Intensive care unit capacity in low-income countries: a systematic review. *PLoS One* 2015; **10**: e0116949 [PMID: 25617837 DOI: 10.1371/journal.pone.0116949]

7 **Vukoja M**, Riviello E, Gavrilovic S, Adhikari NK, Kashyap R, Bhagwanjee S, Gajic O, Kilickaya O; CERTAIN Investigators. A survey on critical care resources and practices in low- and middle-income countries. *Glob Heart* 2014; **9**: 337-42.e1-5 [PMID: 25667185 DOI: 10.1016/j.gheart.2014.08.002]

8 Administrative divisions of India. Available from: https://en.wikipedia.org/wiki/Administrative_divisions_of_India

9 **Amaravadi RK**, Dimick JB, Pronovost PJ, Lipsett PA. ICU nurse-to-patient ratio is associated with complications and resource use after esophagectomy. *Intensive Care Med* 2000; **26**: 1857-1862 [PMID: 11271096 DOI: 10.1007/s001340000720]

10 **Vincent JL**, Marshall JC, Namendys-Silva SA, François B, Martin-Loeches I, Lipman J, Reinhart K, Antonelli M, Pickkers P, Njimi H, Jimenez E, Sakr Y; ICON investigators. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. *Lancet Respir Med* 2014; **2**: 380-

386 [PMID: 24740011 DOI: 10.1016/s2213-2600(14)70061-x]
11 **Pronovost PJ**, Angus DC, Dorman T, Robinson KA, Dremsizov TT, Young TL. Physician staffing patterns and clinical outcomes in critically ill patients: a systematic review. *JAMA* 2002; **288**: 2151-2162 [PMID: 12413375 DOI: 10.1001/jama.288.17.2151]
12 **Groeger JS**, Guntupalli KK, Strosberg M, Halpern N, Raphaely RC, Cerra F, Kaye W. Descriptive analysis of critical care units in the United States: patient characteristics and intensive care unit utilization. *Crit Care Med* 1993; **21**: 279-291 [PMID: 8428482 DOI: 10.1097/00003246-199302000-00022]
13 **Haniffa R**, Isaam I, De Silva AP, Dondorp AM, De Keizer NF. Performance of critical care prognostic scoring systems in low and middle-income countries: a systematic review. *Crit Care* 2018; **22**: 18 [PMID: 29373996 DOI: 10.1186/s13054-017-1930-8]
14 **National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health**. Preventing Tobacco Use Among Youth and Young Adults: A report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); 2012: 16-19 [PMID: 22876391]
15 **Saigal S**, Sharma JP, Pakhare A, Bhaskar S, Dhanuka S, Kumar S, Sabde Y, Bhattacharya P, Joshi R. Mapping the Characteristics of Critical Care Facilities: Assessment, Distribution, and Level of Critical Care Facilities from Central India. *Indian J Crit Care Med* 2017; **21**: 625-633 [PMID: 29142372 DOI: 10.4103/ijccm.IJCCM]
16 **Kashyap R**, Saini C, Vashistha K, Dutt T, Raman D, Bansal V, Seth H, Sharma D, Seshadri P, Singh H, Bhandari G, Ramakrishnan N, Daga M, Gurjar M, Javeri Y. 109: Indian ICU needs assessment survey-1: ININ 2018-I. *Crit Care Explor* 2019; **47**: 37 [DOI: 10.1097/01.ccm.0000550866.81874.58]
17 Distribution of participating intensive care unit's over India's map. *Google Maps*. [accessed December 2019]. Available from: https://www.google.com/maps/d/u/0/edit?mid=1cIgXJUaGSb9afpdR0fv0ee5DWi7EDkkLll=21.715383982952808%2C66.28292755143718z=5

Published by Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 2220-3141 (online)

World Journal of

Critical Care Medicine

World J Crit Care Med 2020 August 7; 9(3): 43-62

Published by Baishideng Publishing Group Inc

World Journal of Critical Care Medicine

Contents

Irregular Volume 9 Number 3 August 7, 2020

ORIGINAL ARTICLE

Retrospective Study

CASE REPORT

World Journal of Critical Care Medicine

Irregular Volume 9 Number 3 August 7, 2020

Contents

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Irregular

EDITORS-IN-CHIEF
KLE Hon

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

PUBLICATION DATE
August 7, 2020

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2020 August 7; 9(3): 43-53

DOI: 10.5492/wjccm.v9.i3.43

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Retrospective Study

Ventilator-associated pneumonia in patients with cancer: Impact of multidrug resistant bacteria

Patricia Cornejo-Juárez, Ivan González-Oros, Paola Mota-Castañeda, Diana Vilar-Compte, Patricia Volkow-Fernández

ORCID number: Patricia Cornejo-Juárez 0000-0001-6331-8372; Ivan González-Oros 0000-0002-7421-2095; Paola Mota-Castañeda 0000-0002-1748-211X; Diana Vilar-Compte 0000-0001-8564-8735; Patricia Volkow-Fernández 0000-0002-1991-0923.

Author contributions: Cornejo-Juárez P designed, made the analysis and wrote the paper; González-Oros I and Mota-Catañeda P performed the research; Vilar-Compte D and Volkow-Fernández P supervised the report and made intellectual contributions.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Instituto Nacional de Cancerología (2019/0096).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data and the confidentiality of the patients was preserved.

Conflict-of-interest statement: All the authors declare do not have conflict of interest.

Patricia Cornejo-Juárez, Ivan González-Oros, Paola Mota-Castañeda, Diana Vilar-Compte, Patricia Volkow-Fernández, Infectious Diseases Department, Instituto Nacional de Cancerología (INCan), Mexico City 14080, Mexico

Corresponding author: Patricia Cornejo-Juárez, MD, MSc, Assistant Professor, Chief Doctor, Infectious Diseases Department, Instituto Nacional de Cancerología (INCan), Av. San Fernando No. 22, Col. Sección XVI, Del. Tlalpan, Mexico City 14080, Mexico. patcornejo@yahoo.com

Abstract

BACKGROUND

Patients with cancer have several risk factors for developing respiratory failure requiring mechanical ventilation (MV). The emergence of multidrug resistant bacteria (MDRB) has become a public health problem, creating a new burden on medical care in hospitals, particularly for patients admitted to the intensive care unit (ICU).

AIM

To describe risk factors for ventilator-acquired pneumonia (VAP) in patients with cancer and to evaluate the impact of MDRB.

METHODS

A retrospective study was performed from January 2016 to December 2018 at a cancer referral center in Mexico City, which included all patients who were admitted to the ICU and required MV ≥ 48 h. They were classified as those who developed VAP versus those who did not; pathogens isolated, including MDRB. Clinical evolution at 60-d was assessed. Descriptive analysis was carried out; comparison was performed between VAP *vs* non-VAP and MDRB *vs* non-MDRB.

RESULTS

Two hundred sixty-three patients were included in the study; mean age was 51.9 years; 52.1% were male; 68.4% had solid tumors. There were 32 episodes of VAP with a rate of 12.2%; 11.5 episodes/1000 ventilation-days. The most frequent bacteria isolated were the following: *Klebsiella* spp. [*n* = 9, four were Extended-Spectrum Beta-Lactamase (ESBL) producers, one was Carbapenem-resistant (CR)]; *Escherichia coli* (*n* = 5, one was ESBL), and *Pseudomonas aeruginosa* (*n* = 8, two were

Manuscript source: Unsolicited manuscript

Received: December 16, 2019
Peer-review started: December 16, 2019
First decision: April 2, 2020
Revised: May 22, 2020
Accepted: June 14, 2020
Article in press: June 14, 2020
Published online: August 7, 2020

P-Reviewer: Gajic O, Santomauro M, Turner AM
S-Editor: Gong ZM
L-Editor: A
E-Editor: Li JH

CR). One Methicillin-susceptible *Staphylococcus aureus* was identified. In multivariate analysis, the sole risk factor associated for VAP was length of ICU stay (OR = 1.1; 95%CI: 1.03-1.17; *P* = 0.003). Sixty-day mortality was 53% in VAP and 43% without VAP (*P* = 0.342). There was not higher mortality in those patients with MDRB.

CONCLUSION
This study highlights the high percentage of Gram-negative bacteria, which allows the initiation of empiric antibiotic coverage for these pathogens. In this retrospective, single center, observational study, MDRB VAP was not directly linked to increased mortality at 60 days.

Key words: Ventilator-associated pneumonia; Cancer; Multidrug resistance bacteria; Mortality; Intensive care unit; Mechanical ventilation

Core tip: This is a retrospective study to evaluate the risk factors for ventilator-associated pneumoniae (VAP) in patients with cancer who are admitted at an intensive care unit and require mechanical ventilation for > 48 h. We emphasized in microbiology etiology, particularly multidrug resistant bacteria (MDRB). We included 263 patients during 2 year-period; 32 developed VAP, with a rate of 11.5 episodes/1000 ventilation-days. Gram-negative bacteria were isolated in 95% of cases, being the rate of MDRB 24.1%. Sixty-day mortality was 53% in VAP and 43% without VAP. There was not higher mortality in patients with MDRB.

Citation: Cornejo-Juárez P, González-Oros I, Mota-Castañeda P, Vilar-Compte D, Volkow-Fernández P. Ventilator-associated pneumonia in patients with cancer: Impact of multidrug resistant bacteria. *World J Crit Care Med* 2020; 9(3): 43-53
URL: https://www.wjgnet.com/2220-3141/full/v9/i3/43.htm
DOI: https://dx.doi.org/10.5492/wjccm.v9.i3.43

INTRODUCTION

The prognosis of malignancies has improved during recent decades, with an increase in overall survival[1,2]. However, patients with cancer have elevated risks of infections and potential complications related with treatment, particularly chemotherapy, central lines, extensive surgeries, and other factors that lead to higher morbidity and mortality[2]. Likewise, patients with cancer have several risk factors for developing respiratory failure related to infectious and non-infectious processes, such as pneumonia, lung thrombosis, sepsis, transfusion-related acute lung injury (TRALI), and lung edema[1]. Therefore, these patients sometimes require support with mechanical ventilation (MV) and admission to the intensive care unit (ICU). The development of Ventilator-Associated Pneumonia (VAP) is the most frequent ICU-acquired infection, occurring in 25%-30% of patients intubated for > 48 h, with an incremental proportional risk within the first 14 d of ventilation[3-5]. The estimated incidence of VAP range from 2-16 episodes per 1000 ventilator-days[5]. On the other hand, the emergence of multidrug resistant bacteria (MDRB) has become a public health problem, creating a new burden on medical care in hospitals, particularly for patients admitted to ICU[6].

The aim of this study was to describe the clinical characteristics, local pathogens included MDRB, risk factors, and outcomes in patients with cancer who develop VAP.

MATERIALS AND METHODS

We conducted a retrospective analysis of all patients admitted to the ICU who required MV for ≥ 48 h at the Instituto Nacional de Cancerología (INCan), a cancer referral center in Mexico City, from January 1st 2016 to December 31st, 2018.

Demographic and clinical data were recorded from the clinical electronic charts of the patients and included the following age; sex; body mass index (BMI); type of neoplasm; current status of cancer (recent diagnosis; complete or partial remission, progression, or relapse); Charlson Comorbidity Index; history of chemotherapy, radiotherapy, biologic drugs, recent hospitalization, or antimicrobials used (during the last 3 mo); Sequential Organ Failure Assessment score (SOFA) and Acute Physiology Age Chronic Health Evaluation (APACHE) II at ICU admission; indication for and days of MV; tracheostomy; bronchial culture or bronchioalveolar lavage; diagnosis of VAP; bacteria isolated that were classified as susceptible, MDRB, or extreme drug-resistant (XDR) bacteria; type and number of days of antimicrobials; length of hospitalization, length of ICU stay, and 60-d outcome.

Pneumonia was clinically suspected on the presence of new and/or progressive pulmonary infiltrates in a chest X-ray, along with two of the following criteria: Hyperthermia (≥ 38 °C) or hypothermia (≤ 36 °C); leukocytosis (≥ 12000/mL) or leucopenia (≤ 4000/mL), and purulent pulmonary secretions[7,8].

VAP was defined as pneumonia in a patient on mechanical ventilation for > 2 calendar days on the day of event, with day of ventilator placement being Day 1 and the ventilator was in place on the date of event of the day before[9]. In those patients who were admitted to the ICU with pre-existing pneumonia, the clinical worsening, and/or the appearance of new clinical data compatible with pneumonia criteria were considered to be redefined as VAP.

Endotracheal aspirate or sputum cultures together with blood cultures were performed on day one the ICU stay and later in the case of clinical deterioration or suspected pneumonia. Bronchial samples were taken by sterile aspiration through the endotracheal tube and inoculated on blood, MacConkey, Sabouraud, and chocolate agar. Bacterial identification was performed by Mass Spectrometry Especially Matrix-Assisted Laser Desorption and Ionization -Time of Flight- Mass Spectrometry (MALDI-TOF-MS; Microflex, United States). Antimicrobial susceptibility testing was performed by means of BD Automated Phoenix™ (United States) and by the Kirby-Bauer disk diffusion technique in the case of resistant strains (Clinical Laboratory Standards Institute. Microbiological data were collected from the patient's electronic clinical chart and from Microbiology Laboratory data including cultures from the lower respiratory tract (sputum, tracheal, bronchial aspirate, or bronchioalveolar lavage). Polymicrobial pneumonia was defined when more than one pathogen was identified. The presence of MDR/XDR pathogens was recorded and defined according to Magiorakos criteria[10].

Primary outcome was VAP development. Secondary outcome was clinical evolution at 60-d.

Statistical analysis

Descriptive analysis was carried out with mean ± SD or median [Interquartile range (IQR)]. The student *t*-test or the Mann-Whitney *U* test were used to compare continuous variables as appropriate. The χ^2 or Fisher exact test was utilized to compare categorical variables. Variables with *P* values of ≤ 0.3 in the univariate analysis were included in the multivariate analysis. A logistic regression model was performed for risk factors associated with VAP and for 60-day mortality. OR with 95%CI were calculated. *P* values of ≤ 0.05 were considered statistically significant. Data was analyzed using STATA (ver. 14) software. The study was approved by the INCan Institutional Review Board (REF/INCAN/CI/0922/2019).

RESULTS

Patient characteristics

During the study period, 736 patients were admitted to the ICU: 345 patients required MV for less than 48 h and 128 did not require intubation; 263 patients were included. Mean age was 51.9 ± 17.8 years; 188 (68.4%) were patients with solid tumors and there were 88 (31.8%) with hematologic malignancies; 123 (46.8%) were in cancer progression or relapse; eight patients had two different neoplasms. Other demographic and clinical data are shown in Table 1.

The main cause for MV was septic shock (*n* = 91, 34.6%), followed by post-surgical procedure (*n* = 42, 16%), pneumonia (*n* = 38, 14.5%), and hypovolemic shock (*n* = 37, 14.1%). The median length of MV was 8 d (IQR 4, 12 d).

Table 1 Clinical and demographic characteristics of all patients with mechanical ventilation during the study period (*n* = 263)

Characteristics, *n* (%)	Total (*n* = 263)	VAP (*n* = 32)	Non-VAP (*n* = 231)	*P* value
Age (yr)[1]	51.9 ± 17.8	49 ± 19.7	52.3 ± 17.5	0.329
Gender- Masculine	137 (52.1)	16 (50)	110 (47.6)	0.800
Body mass index[1]	26.2 ± 5.6	24.9 ± 4.5	26.4 ± 5.7	0.188
Solid tumor[2]	188 (68.1)	25 (67.6)	163 (68.2)	0.938
Cervical	21 (7.6)	2 (5.4)	19 (7.9)	0.749
Head and neck	21 (7.6)	3 (8.1)	18 (7.5)	1
Colon-rectum	20 (7.2)	1 (2.7)	19 (7.9)	0.492
Breast	18 (6.5)	2 (5.4)	16 (6.7)	1
Germinal	15 (5.4)	2 (5.4)	13 (5.4)	1
Esophagus-stomach	14 (5.1)	3 (8.1)	11 (4.6)	0.399
Sarcoma	13 (4.7)	2 (5.4)	11 (4.6)	0.688
Ovarian	10 (3.6)	1 (2.7)	9 (3.8)	1
Lung	10 (3.6)	1 (2.7)	9 (3.8)	1
Prostate	9 (3.3)	2 (5.4)	7 (2.9)	0.348
Liver and bile ducts	9 (3.3)	1 (2.7)	8 (3.3)	1
Pancreas	7 (2.5)	1 (2.7)	6 (2.5)	1
Kidney and bladder	5 (1.8)	2 (5.4)	3 (1.3)	0.136
Other	16 (5.8)	2 (5.4)	14 (5.9)	1
Hematological malignancies[2]	88 (31.9)	12 (32.4)	76 (31.8)	0.938
Lymphoblastic leukemia	26 (9.4)	3 (8.1)	23 (9.6)	1
Myeloid leukemia	12 (4.3)	3 (8.1)	9 (3.8)	0.207
Non-Hodgkin lymphoma	25 (9.1)	2 (5.4)	23 (9.6)	0.548
Hodgkin lymphoma	4 (1.5)	1 (2.7)	3 (1.2)	0.439
Multiple myeloma	14 (5.1)	2 (5.4)	12 (5)	1
Other[3]	7 (2.5)	1 (2.7)	6 (2.5)	1
Cancer stage				
Recent diagnosis	117 (44.5)	11(34.4)	105 (45.4)	0.236
Progression	93 (35.4)	16 (50)	78 (33.8)	0.07
Relapse	30 (11.4)	2 (6.2)	28 (12.1)	0.551
Partial remission	21 (8)	2 (6.2)	19 (8.2)	1
Complete remission	2 (0.7)	1 (3.1)	1 (0.4)	0.228
Chemotherapy within 3 mo	99 (37.6)	16 (50)	83 (35.9)	0.123
Radiotherapy during the previous 6 mo	23 (8.7)	3 (94)	20 (8.7)	0.749
Biologic antineoplastic drugs	22 (8.4)	6 (18.8)	16 (6.9)	0.155
Charlson index	3 (2, 5)	3 (2, 5)	3 (2, 5)	1
Hospital admission within 3-mo period	75 (28.5)	5 (15.6)	70 (30.3)	0.09
Days of recent hospitalization[4]	7 (4,12)	5 (4,9)	7 (4,12)	0.544
Recent broad antimicrobials	36 (13.7)	1 (3.1)	35 (15.1)	0.09

[1]Median ± SD.
[2]Percentage was obtained from 276 patients because 13 patients had two different neoplasms (5 in VAP group and 8 in Non-VAP).
[3]Four had myelodysplastic syndrome, three had chronic leukemia.

[4]Median (Interquartile range). VAP: Ventilator-associated pneumonia.

Risk factors for VAP

There were 32 episodes of VAP; the rate was 12.2%, with an incidence of 11.5 episodes/1000 ventilation-days. Mean days of MV until VAP diagnosis was 13.1 ± 8.8. d (Table 2).

There was a statistically significant difference between median length of ICU stay in patients with VAP (18 d; IQR 9, 27) *vs* those without VAP (8 d; IQR 5, 12; $P < 0.001$). Also, there was a difference in median length of hospitalization (32 d for VAP; IQR 22, 57 d *vs* 21 d for non-VAP; IQR 14, 32; $P < 0.001$). Mean duration of MV was significantly longer in those who developed VAP (16 d; IQR 9, 27) *vs* those who did not (7 d; IQR 4, 11; $P < 0.001$). Data is shown in Table 2.

There were no differences between age, gender, solid or hematological neoplasm, recent chemotherapy, progression or relapse in those who developed VAP *vs* those who did not. The uni- and multivariate analysis is point in Table 3.

Pathogens

There were 42 bacteria identified in patients with VAP. In 16 (50%), only one pathogen was isolated, 11 were polymicrobial (seven cultures with two different pathogens, four with three), and five cultures were negative. The most frequent bacteria isolated were as follows: *Klebsiella* spp. ($n = 9$, 21.4%), four (44.4%) were Extended-Spectrum Beta-Lactamases (ESBL) producers, and one (11.1%) was Carbapenem-resistant (CR); *Escherichia coli* ($n = 5$, 11.9%), one (25%) was ESBL producer; Pse*udomonas aeruginosa* ($n = 8$, 19%), two (25%) were CR; and *Enterobacter* spp. ($n = 6$, 14.3%), among which none was resistant. There were two Gram-positive bacteria identified: one *Enterococcus faecalis* and one Methicillin-susceptible *Staphylococcus aureus* (MSSA) (Figure 1). The rate of MDRB was 24%. There were no differences when comparing MDRB *vs* susceptible, length of hospitalization, previous antibiotics, or days of MV. Patients with MDRB had a longer stay at the ICU (14.1 ± 11 d) *vs* patients with susceptible bacteria (10.1 ± 7.8 d; $P = 0.02$).

Patients who developed VAP more frequently received cephalosporins, carbapenems, Tazobactam/Piperacillin, Vancomycin, and fluoroquinolones; furthermore, the period of administration of carbapenems was longer (Table 4).

Risk factors for VAP

Univariate analysis comparing patients with VAP *vs* non-VAP revealed that tracheostomy and re-intubation were more frequent in VAP (27.9% *vs* 6.6%; $P < 0.001$, and 28% *vs* 10.6%; $P = 0.03$, respectively). Median length of hospitalization was longer for VAP *vs* non-VAP (32 d; IQR 21, 57 d *vs* 21 d *vs* IQR 14, 32; $P < 0.001$), in addition, the median length of ICU stay was 18 d (IQR 9, 27 *vs* 8 d *vs* IQR 5, 12; $P < 0.001$), and median days of MV was VAP 16 d (IQR 9, 27 *vs* non-VAP 7 d; IQR 4, 11; $P < 0.001$). In multivariate analysis, only length of ICU stay was found statistically significant (OR = 1.11; 95%CI: 1.06-1.17; $P < 0.001$)(Table 3).

Risk factors for mortality

One hundred sixteen patients (44.1%) died during the first 60 d: 17 (53%) with VAP *vs* 99 (43%) without VAP ($P = 0.342$). No differences were found between hematologic patients ($n = 42$, 47.7%), *vs* those with solid tumors ($n = 74$, 42.3%; $P = 0.401$). There was no difference in outcome in patients with MDRB ($P = 1$). Univariate and multivariate analysis demonstrated that a recent history of chemotherapy (OR = 2.16; 95%CI: 1.24-3.76) and tracheostomy (OR = 2.52; 95%CI: 1.24-5.13) were predictive risk factors for 60-d mortality (Table 5).

DISCUSSION

This study sought to describe the characteristics of patients with cancer admitted to the ICU who required MV and developed VAP, analyzing risk factors for 60-d mortality.

It is important to note that almost two thirds of the patients had a solid tumor and one third had received chemotherapy within the last 3 mo. It is relevant to highlight that 46.8% of patients were on cancer relapse or progression, because policies in our

Table 2 Clinical data related with current hospitalization and mechanical ventilation (*n* = 263)

Characteristic – *n* (%)	Total (*n* = 263)	VAP (*n* = 32)	Non-VAP (*n* = 231)	*P* value
Length of hospitalization (d)[1]	22 (14, 34)	32 (22, 57)	21 (14, 32)	0.0001
Length of ICU stay (d)[1]	8 (5, 13)	18 (9, 27)	8 (5, 12)	< 0.0001
Causes for MV				
Septic shock	91 (34.6)	10 (31.3)	81 (35)	0.843
Post-surgical procedure	42 (16)	8 (25)	34 (14.7)	0.193
Respiratory failure secondary to pneumonia	37 (14)	3 (9.4)	34 (14.7)	0.589
Hypovolemic shock	37 (14)	8 (25)	29 (12.5)	0.09
Neurologic cause	13 (4.9)	0	13 (5.6)	N/A
Lung tumor activity	7 (2.7)	1 (3.1)	6 (2.6)	0.601
Post-CPR	7 (2.7)	1 (3.1)	6 (2.6)	0.601
Acute pulmonary edema	6 (2.3)	0	6 (2.6)	N/A
Malignant central airway obstruction	5 (1.9)	0	5 (2.2)	N/A
Cardiac failure	3 (1.1)	1 (3.1)	2 (0.8)	0.323
Bronchospasm	2 (0.8)	0	2 (0.8)	N/A
Pulmonary embolism	2 (0.8)	0	2 (0.8)	N/A
TRALI	1 (0.4)	0	1 (0.4)	N/A
Other causes	10 (3.8)	0	10 (4.3)	N/A
SOFA at ICU admission[2]	8.3 ± 3.4	8.7 ± 2.8	8.3 ± 3.4	0.477
Days of mechanical ventilation[1]	8 (4, 12)	16 (9, 27)	7 (4, 11)	< 0.0001
Tracheostomy	68 (25.9)	19 (59.4)	49 (21.2)	< 0.0001
Re-intubation	27 (10.3)	7 (21.9)	20 (8.7)	0.03
Mortality at 60 d	116 (44.1)	9 (28.1)	72 (31.7)	0.839

[1]Median (Interquartile range).
[2]mean ± SD. CPR: Cardiopulmonary resuscitation; N/A: Not applicable; TRALI: Transfusion-related acute lung injury; ICU: Intensive care unit; SOFA: Sequential Organ Failure Assessment score; MV: Mechanical ventilation; VAP: Ventilator-associated pneumonia.

hospital include the admission at the ICU of patients who have an expectation of survival more than 3 mo, an adequate functional state, and if they are receiving the first or second line of neoplastic treatment even if they are not in remission. Regarding the risk factors analyzed in relation to cancer such as solid tumor *vs* hematological, clinical stage of cancer, or recent chemotherapy, there was no relationship with the development of VAP. The median of Charlson Comorbidity Index was 3 for the whole group, that corresponds to one-year mortality rate of 52%. SOFA index was less than 10 in all patients, without differences between VAP *vs* non-VAP, that indicates between one or two organ failures, and a mortality percentage between 10% and 25%.

The incidence of VAP varies among different series, the latter related to the characteristics of ICU and type of hospitals, and ranges between 2.1 and 24.5 cases/1000 ventilator-days[4,11]. Specifically, a study performed in patients with cancer, VAP was reported in 42/1000 ventilator-days[11]. The incidence we found in this study was 12.2% and 11.5 cases/1000 ventilator-days, lower than those reported in these previous studies[4,11].

VAP is associated with longer hospital and ICU stays, higher hospital-related costs, and greater in-hospital mortality[4]. We also described longer ICU and hospital stays and more days of MV in patients with VAP, more often requiring tracheostomy and re-intubation. These findings would be explained by effect-cause bias, because patients with VAP are patients who are more difficult to extubate, they require a tracheostomy more frequently, more days of antibiotics, and this leads to more days of hospitalization. An important finding in this study was that patients with VAP more frequently received broad-spectrum antibiotics (particularly cephalosporins,

Table 3 Univariate and multivariate analysis for ventilator-associated pneumonia in patients with mechanical ventilation (*n* = 263)

Characteristics	Univariate			Multivariate	
	NAV (*n* = 32)	No-NAV (*n* = 231)	*P* value	OR	*P* value
Female	16 (50)	121 (52.4)	0.8	-	
Male	16 (50)	110 (47.6)			
Age < 60 yr	21 (65.6)	134 (58)	0.411	-	
Age ≥ 60 yr	11 (34.4)	97 (42)			
Solid tumor	12 (37.5)	76 (32.9)	0.605	-	
Hematologic malignancy	20 (62.5)	155 (67.1)			
Recent diagnosis, complete or partial remission	14 (43.8)	125 (54.1)	0.271	1	0.541
Progression or relapse	18 (56.2)	106 (45.9)		1.3 (0.55 - 3.03)	
Non-recent chemotherapy	16 (50)	148 (64.1)	0.123	1	0.727
Recent chemotherapy	16 (50)	83 (35.9)		1.16 (0.49-2.76)	
SOFA at ICU admission	8.71 ± 2.79	8.26 ± 3.42	0.477	-	
Days of hospitalization length[1]	32 (22, 57)	21 (14, 32)	0.0001	1	0.301
				1 (0.99- 1.01)	
Days of ICU length[1]	18 (9, 27)	8 (5, 12)	< 0.0001	1	< 0.0001
				1.11 (1.06-1.17)	
Alive	10 (31.2)	122 (52.8)	0.02	1	0.125
Death	22 (68.8)	109 (47.2)		2.04 (0.82-5.12)	

[1]Median (Interquartile range). ICU: Intensive care unit.

Tazobactam/Piperacillin, carbapenems, and Vancomycin). It is noteworthy that frequent causes for ICU admission were septic shock and respiratory failure secondary to pneumonia; thus, broad-spectrum antibiotics are usually initiated empirically in these patients.

Some studies have described Gram-negative bacilli as the most common group of VAP-associated pathogens, accounting for over 50% of cases; *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, in addition to *S. aureus*[4,12]. We found that 95% of Gram-negative bacteria in this series were *Klebsiella* spp., *P. aeruginosa*, *Enterobacter* spp., and *E. coli* the most common pathogens. It is important to emphasize that there were only two Gram-positive bacteria identified. Additionally, we found that 34.3% of the infections were polymicrobial, similar to 40% reported in other studies[3].

Likewise, an increase has been described in the isolation of Gram-negative MDRB strains in patients with VAP[13]. Nevertheless, we identified only 21.4% of MDRB strains as follows: ESBL-*Klebsiella* spp. in 44.4%; ESBL-*E. coli* in 25%; *P. aeruginosa* CR in 25%, and *Klebsiella* spp. in 11.1%. The rate of MDRB described in this study was similar to that which we have previously reported in health care-associated infections in the same ICU during 2013 and 2014 (24%)[14]. The National Healthcare Surveillance Network in the United States in 2014 found the following higher rates of MDR in patients with VAP: 37% of Methicillin-resistant *S. aureus* (MRSA); 31.1% CR-*P. aeruginosa*, and 14% CR-*Klebsiella pneumoniae*. A study performed to assess the microbiological profile and MDR Gram-negative bacteria in the ICU during 2010-2011, showed *Citrobacter* and K. pneumoniae as the most common isolated pathogens, with a high prevalence of carbapenemase- producing bacteria (48%)[15], considerably higher than the results found in our study.

MDRB strains have been related with widespread use of antimicrobials, prolonged use of MV, longer length of hospitalization, and prior antibiotic therapy[12]. In this study, only longer ICU stay was more frequent in patients with these bacteria (*P* = 0.02).

Sixty-day mortality was reported in 44.1% (48.8% in hematological and 43.4% in patients with solid tumors; *P* = 0.457). In a previous study performed in the same ICU, the mortality rate for patients with MV was 34.4% (73% for hematological patients and

Table 4 Use of antimicrobials in patients with ventilator-associated pneumonia *vs* those who did not develop the latter

Antimicrobial treatment	Total (*n* = 263)	Non-VAP (*n* = 233)	VAP (*n* = 30)	*P* value
Antibacterial treatment				
Cephalosporins	58 (22)	47 (20.2)	11 (36.7)	0.03
Days of cephalosporins[12]	6 (4, 9)	6 (4, 9)	4 (4, 10)	0.856
TZP	86 (32.6)	69 (29.6)	17 (56.7)	0.002
Days of TZP[2]	6 (4, 9)	7 (4, 9)	6 (5, 7)	0.895
Aminoglycosides	18 (6.8)	14 (6)	4 (13.3)	0.134
Days of aminoglycosides[2]	4 (3, 6)	3 (3, 5)	5 (4, 7)	0.469
Carbapenem	228 (86.7)	198 (85)	30 (100)	0.02
Days of Carbapenem[2]	11 (7, 17)	10 (6, 16)	13 (10, 22)	0.003
Fluoroquinolones	31 (11.8)	23 (9.9)	8 (26.7)	0.006
Days of fluoroquinolones[2]	10 (7, 14)	11 (7, 14)	9 (5, 15)	0.586
Vancomycin	153 (58.2)	130 (55.8)	24 (80)	0.01
Days of vancomycin[2]	7 (4, 10)	7 (4, 10)	7 (4, 10)	0.684
Linezolid	47 (17.8)	39 (16.7)	8 (26.7)	0.205
Days of linezolid[2]	9 (5, 12)	8 (4, 11)	14 (8, 21)	0.05
Clarithromycin	68 (25.8)	59 (25.3)	9 (30)	0.657
Days of clarithromycin[2]	8 (7, 10)	8 (6, 10)	8 (8,10)	0.505
SMX/TMP	68 (25.8)	56 (24)	12 (40)	0.06
Days of SMX/TMP[2]	8 (5, 13)	12 (7, 21)	12 (8, 14)	0.577
Colistin	11 (4.2)	7 (3)	4 (13.3)	0.02
Days of colistin[2]	10 (4, 11)	8 (3, 11)	11 (8, 12)	0.341

[1]Third-generation.
[2]Median (Interquartile range). TZP: Piperacillin/tazobactam; VAP: Ventilator-associated pneumonia.

34.3% for patients with solid tumors)[16], this lower mortality can be related because, in the last study, we included all patients with MV, regardless of ventilation time.

Bundle implementation reduces the rate of VAP; this is the most efficacious measure when compliance rates are high, and includes education and training, hand hygiene, head positioning (> 30º), cuff- pressure maintenance, avoidance of elective changes of circuits, humidifiers, and endotracheal tubes, oral chlorhexidine gluconate, aspiration of subglottic secretions, selective decontamination of the oropharynx tract, and a short course of systemic antibiotics during the intubation of patients with previous decreased consciousness[17,18]. In our hospital, the previous measures, except for the last two, are performed routinely; adherence to prevention bundles is monitored by a nurse from the Infection Control Department who is assigned to the ICU. In addition to the latter prevention measures, enhancing antimicrobial stewardship programs is a simple and cost-effective way to improve clinical outcomes, maintaining quality of care and contributing to the decrease of VAP episodes[19].

There are some imitations of this study. First, it was retrospective, and second was conducted at only one center, it could have the bias inherent to this type of design. However, the hospital is one of the biggest in the region, and the number of patients treated each year is also large. Third, the number of episodes of VAP were not many, which could have influenced not to find significant differences in some of the risk factors studied. On the other hand, the study's main strength is the example of how a study such as the one we present, contributes to reinforcing policies of antimicrobial stewardship within a hospital tailored by the results.

In conclusion, the rate of VAP was similar to that reported in other studies conducted in immunosuppressed patients. However, it is important to highlight the elevated percentage of Gram-negative bacteria as a cause of pneumonia, which permits beginning empiric antibiotic coverage for these pathogens, without the need to

Table 5 Univariate and multivariate analysis for 60-d mortality in patients with mechanical ventilation (*n* = 263)

Characteristics	Univariate			Multivariate	
	Alive (*n* = 147)	Death (*n* = 116)	*P* value	OR	*P* value
Female	79 (53.7)	58 (50)	0.546	-	
Male	68 (46.3)	58 (50)			
Age < 60 yr	83 (56.5)	72 (62.1)	0.358	-	
Age ≥ 60 yr	64 (43.5)	44 (37.9)			
Solid tumor	101 (68.7)	74 (63.8)	0.401	-	
Hematologic malignancy	46 (31.3)	42 (36.2)			
Recent diagnosis, complete or partial remission	85 (57.8)	54 (46.6)	0.069	1	0.237
Progression or relapse	62 (42.2)	62 (53.4)		1.38 (0.81-2.37)	
Non-recent chemotherapy	103 (70.1)	61 (52.6)	0.003	1	0.006
Recent chemotherapy	44 (29.9)	55 (47.4)		2.16 (1.24-3.76)	
SOFA at ICU admission	8.45 ± 3.45	8.15 ± 3.2	0.471	-	
Non-tracheostomy	115 (78.2)	80 (69)	0.088	1	0.01
Required tracheostomy	32 (21.8)	36 (31)		2.52 (1.24-5.13)	
Days of ICU length	8 (6, 13)	8 (5, 15)	0.457	-	
Days of mechanical ventilation	7 (4, 11)	9 (5, 14)	0.029	1	0.15
				1.04 (1.008-1.07)	
Non-VAP	132 (89.8)	99 (85.3)	0.342	-	
VAP	15 (10.2)	17 (14.7)			

ICU: Intensive care unit; SOFA: Sequential Organ Failure Assessment score; VAP: Ventilator-acquired pneumonia.

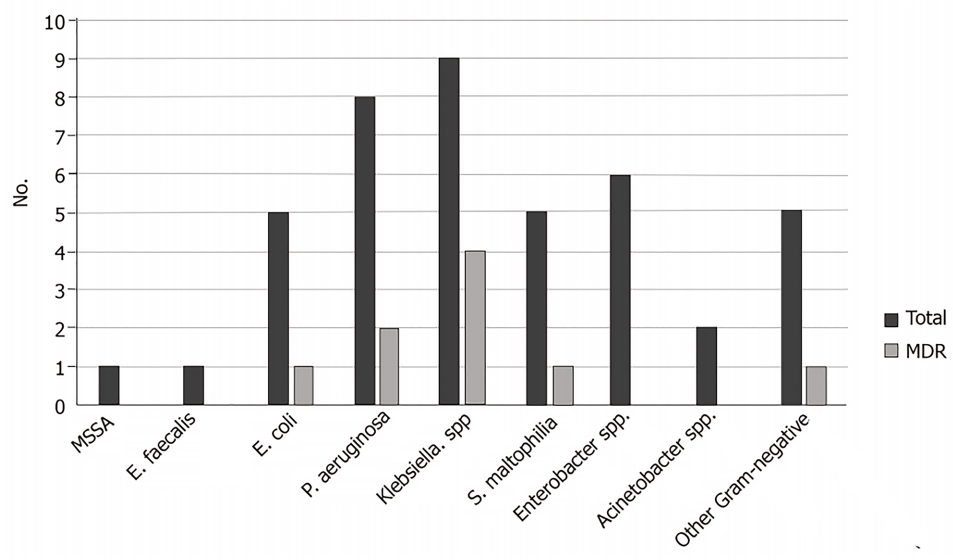

Figure 1 Pathogens isolated from patients with ventilator-acquired pneumonia in patients with cancer including multidrug resistant bacteria. MDR: Multidrug resistant.

cover Gram-positive bacteria, particularly Vancomycin for Methicillin-resistant *S. aureus*. In this retrospective, single center, observational study, MDRB VAP was not directly linked to increased mortality at 60 d.

ARTICLE HIGHLIGHTS

Research background

Patients with cancer have several risk factors for developing respiratory failure requiring mechanical ventilation (MV). The emergence of multidrug resistant bacteria (MDRB) has become a public health problem, creating a new burden on medical care in hospitals, particularly for patients admitted to the intensive care unit (ICU).

Research motivation

To establish and/or modify guidelines for the initiation of empirical antimicrobial treatment in cancer patients who develop VAP.

Research objectives

To describe in the patient with cancer which are the risk factors for developing ventilator-acquired pneumonia, and if there is a higher incidence of episodes secondary to multidrug-resistant bacteria.

Research methods

A retrospective study carried out over a two-year period, that included all patients with mechanical ventilation who were admitted to the ICU, and we analyzed those who developed an episode of VAP and the bacteria involved.

Research results

Two hundred sixty-three patients were included; two thirds with a solid tumor. There were 32 episodes of VAP; 11.5 episodes/1000 ventilation-days. Gram-negative bacteria were involved in 95%of cases, 24% were MDRB. There were no differences in mortality between those patients with VAP *vs* non-VAP, neither when MDRB *vs* non-MDRB were compared. Length of ICU was documented as risk factor for VAP. Recent chemotherapy and tracheostomy were predictive risk factors for 60-d mortality.

Research conclusions

The rate of VAP was similar to that reported in other studies. We described an elevated percentage of Gram-negative bacteria as a cause of pneumonia, which permits beginning empiric antibiotic coverage for these pathogens. MDRB were found in a quarter of the episodes, and were not linked to increased mortality at 60 d.

Research perspectives

To perform a monitoring for a longer period of time will allow evaluating the evolution of bacterial resistance, and establishing whether, with a greater number of cases, it can impact the mortality of these patients.

ACKNOWLEDGEMENTS

Infection Control and Hospital Epidemiology Team.

REFERENCES

1 **Belenguer-Muncharaz A**, Albert-Rodrigo L, Ferrandiz-Sellés A, Cebrián-Graullera G. [Ten-year evolution of mechanical ventilation in acute respiratory failure in the hematogical patient admitted to the intensive care unit]. *Med Intensiva* 2013; **37**: 452-460 [PMID: 23890541 DOI: 10.1016/j.medin.2012.12.011]

2 **Park SA**, Cho SS, Kwak GJ. Factors influencing ventilator-associated pneumonia in cancer patients. *Asian Pac J Cancer Prev* 2014; **15**: 5787-5791 [PMID: 25081653 DOI: 10.7314/apjcp.2014.15.14.5787]

3 **Patil HV**, Patil VC. Incidence, bacteriology, and clinical outcome of ventilator-associated pneumonia at tertiary care hospital. *J Nat Sci Biol Med* 2017; **8**: 46-55 [PMID: 28250674 DOI: 10.4103/0976-9668.198360]

4 **Liu Y**, Di Y, Fu S. Risk factors for ventilator-associated pneumonia among patients undergoing major oncological surgery for head and neck cancer. *Front Med* 2017; **11**: 239-246 [PMID: 28493197 DOI: 10.1007/s11684-017-0509-8]

5 **Sarda C**, Fazal F, Rello J. Management of ventilator-associated pneumonia (VAP) caused by resistant gram-negative bacteria: which is the best strategy to treat? *Expert Rev Respir Med* 2019; **13**: 787-798 [PMID: 31210549 DOI: 10.1080/17476348.2019.1632195]

6 **Aly NY**, Al-Mousa HH, Al Asar el SM. Nosocomial infections in a medical-surgical intensive care unit. *Med Princ Pract* 2008; **17**: 373-377 [PMID: 18685276 DOI: 10.1159/000141500]

7 **Kalil AC**, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, Napolitano LM, O'Grady NP, Bartlett JG, Carratalà J, El Solh AA, Ewig S, Fey PD, File TM Jr, Restrepo MI, Roberts JA, Waterer GW, Cruse P, Knight SL, Brozek JL. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016; **63**: e61-e111 [PMID: 27418577 DOI: 10.1093/cid/ciw353]

8 **Nair GB**, Niederman MS. Ventilator-associated pneumonia: present understanding and ongoing debates. *Intensive Care Med* 2015; **41**: 34-48 [PMID: 25427866 DOI: 10.1007/s00134-014-3564-5]

9 **Centers for Disease Control and Prevention**. Pneumonia (Ventilator-associated [VAP] and non-ventilator-associated Pneumonia [PNEU]) Event. [published January 2020]. Available from: https://www.cdc.gov/nhsn/pdfs/pscmanual/6pscvapcurrent.pdf

10 **Magiorakos AP**, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012; **18**: 268-281 [PMID: 21793988 DOI: 10.111/j.1469-0691.2011.03570.x]

11 **Stoclin A**, Rotolo F, Hicheri Y, Mons M, Chachaty E, Gachot B, Pignon JP, Wartelle M, Blot F. Ventilator-associated pneumonia and bloodstream infections in intensive care unit cancer patients: a retrospective 12-year study on 3388 prospectively monitored patients. *Support Care Cancer* 2020; **28**: 193-200 [PMID: 31001694 DOI: 10.1007/s00520-019-04800-6]

12 **Yalçınsoy M**, Salturk C, Takır HB, Kutlu SB, Oguz A, Aksoy E, Balcı M, Kargın F, Mocin OY, Adıguzel N, Gungor G, Karakurt Z. Case fatality rate related to nosocomial and ventilator-associated pneumonia in an ICU: a single-centre retrospective cohort study. *Wien Klin Wochenschr* 2016; **128**: 95-101 [PMID: 26542131 DOI: 10.1007/s00508-015-0884-6]

13 **Roberts KL**, Micek ST, Juang P, Kollef MH. Controversies and advances in the management of ventilator associated pneumonia. *Expert Rev Respir Med* 2017; **11**: 875-884 [PMID: 28891372 DOI: 10.1080/17476348.2017.1378574]

14 **Cornejo-Juárez P**, Vilar-Compte D, García-Horton A, López-Velázquez M, Ñamendys-Silva S, Volkow-Fernández P. Hospital-acquired infections at an oncological intensive care cancer unit: differences between solid and hematological cancer patients. *BMC Infect Dis* 2016; **16**: 274 [PMID: 27286681 DOI: 10.1186/s12879-016-1592-1]

15 **Thakuria B**, Singh P, Agrawal S, Asthana V. Profile of infective microorganisms causing ventilator-associated pneumonia: A clinical study from resource limited intensive care unit. *J Anaesthesiol Clin Pharmacol* 2013; **29**: 361-366 [PMID: 24106362 DOI: 10.4103/0970-9185.117111]

16 **Namendys-Silva SA**, Jarquin-Badiola YD, García-Guillén FJ, Texcocano-Becerra J, Cázares-Mejía R, Herrera-Gómez A. Mechanical ventilation in critically ill cancer patients. *Heart Lung* 2015; **44**: 85-86 [PMID: 25455912 DOI: 10.1016/j.hrtlng.2014.09.004]

17 **Ochoa-Hein E**, Choi SJ, Gómez-Santillán JA, Oyervides-Alvarado JA, Galindo-Fraga A, Rivero-Sigarroa E, Hernández-Gilsoul T, Domínguez-Cherit JG. Near-zero ventilator-associated pneumonia rates after implementation of a multimodal preventive strategy in a Mexican hospital. *Am J Infect Control* 2020; **48**: 446-447 [PMID: 31677926 DOI: 10.1016/j.ajic.2019.09.018]

18 **O'Grady NP**, Murray PR, Ames N. Preventing ventilator-associated pneumonia: does the evidence support the practice? *JAMA* 2012; **307**: 2534-2539 [PMID: 22797453 DOI: 10.1001/jama.2012.6445]

19 **Borgatta B**, Rello J. How to approach and treat VAP in ICU patients. *BMC Infect Dis* 2014; **14**: 211 [PMID: 25430899 DOI: 10.1186/1471-2334-14-211]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2020 August 7; 9(3): 54-62

DOI: 10.5492/wjccm.v9.i3.54

ISSN 2220-3141 (online)

CASE REPORT

Lessons from a methanol poisoning outbreak in Egypt: Six case reports

Ahmed S Gouda, Amr M Khattab, Bruno Mégarbane

ORCID number: Ahmed S Gouda 0000-0003-2470-0792; Amr M Khattab 0000-0001-8560-2745; Bruno Mégarbane 0000-0002-2522-2764.

Author contributions: Gouda AS and Khattab AM managed the patients; Gouda AS and Mégarbane B developed the framework of the paper; Gouda AS wrote the first draft; Mégarbane B worked on subsequent drafts; all authors confirmed the last version before submission, and read and approved the final manuscript.

Informed consent statement: The patients gave their written informed consents.

Conflict-of-interest statement: The authors have no conflicts of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Ahmed S Gouda, National Egyptian Center of Environmental and Toxicological Research, Faculty of Medicine, Cairo University, Cairo 11562, Egypt

Amr M Khattab, Department of Forensic Medicine and clinical Toxicology, Faculty of Medicine, Cairo University, Cairo 11562, Egypt

Bruno Mégarbane, Department of Medical and Toxicological Critical Care, Lariboisière Hospital, Paris 75010, France

Corresponding author: Bruno Mégarbane, MD, PhD, Professor, Department of Medical and Toxicological Critical Care, Lariboisière Hospital, 2 Rue Ambroise Paré, Paris 75010, France. bruno.megarbane@lrb.aphp.fr

Abstract

BACKGROUND

Mass methanol poisonings are challenging, especially in regions with no preparedness, management guidelines and available antidotes.

CASE SUMMARY

Six Ukrainian patients were referred to our emergency department in Cairo, Egypt several hours after drinking an alcoholic beverage made of 70%-ethanol disinfectant bought from a local pharmacy. All patients presented with severe metabolic acidosis and visual impairments. Two were comatose. Management was based on the clinical features and chemistry tests due to deficient resources for methanol leveling. No antidote was administered due to fomepizole unavailability and the difficulties expected to obtain ethanol and safely administer it without concentration monitoring. One patient died from multiorgan failure, another developed blindness and the four other patients rapidly improved.

CONCLUSION

This methanol poisoning outbreak strongly highlights the lack of safety from hazardous pharmaceuticals sold in pharmacies and limitations due to the lack of diagnostic testing, antidote availability and staff training in countries with limited-resources such as Egypt.

Key words: Hemodialysis; Limited resources; Methanol; Metabolic acidosis; Outbreak; Poisoning; Case report

Manuscript source: Invited manuscript

Received: April 6, 2020
Peer-review started: April 6, 2020
First decision: June 8, 2020
Revised: June 8, 2020
Accepted: July 19, 2020
Article in press: July 19, 2020
Published online: August 7, 2020

P-Reviewer: Tabaran F
S-Editor: Ma YJ
L-Editor: Filipodia
E-Editor: Li JH

Core tip: Mass methanol poisoning with unpredictable risk assessment represents a major threat in developing countries. This work reports a clinical series with patients' features and outcome, describes the investigations to identify rapidly the involved causative agent (here, a homemade beverage made with alcoholic disinfectant) and discusses the observed insufficiencies to improve hospital preparedness in case of methanol poisoning outbreak.

Citation: Gouda AS, Khattab AM, Mégarbane B. Lessons from a methanol poisoning outbreak in Egypt: Six case reports. *World J Crit Care Med* 2020; 9(3): 54-62
URL: https://www.wjgnet.com/2220-3141/full/v9/i3/54.htm
DOI: https://dx.doi.org/10.5492/wjccm.v9.i3.54

INTRODUCTION

Methanol is included in many home chemicals, fluids, varnishes, stains and dyes. Toxicity results from its metabolism by alcohol dehydrogenase (ADH) to formic acid, which accumulates and results in metabolic acidosis and organ injuries (Figure 1)[1]. Small ingested amounts as little as 10 mL of pure methanol may be sufficient to cause life-threatening toxicity and permanent blindness[2].

Acute single-patient methanol poisonings are commonly reported while outbreaks occur sporadically, especially in countries with limited accessibility to ethanol due to unavailability or religious, cultural and economic reasons. Methanol is consumed accidentally as ethanol substitute in underground homemade alcoholic beverages[3-6]. Methanol poisoning outbreaks have also been reported in occidental countries resulting in hundreds of victims and deaths[7-10]. In such epidemics, providing effective therapy on time may be challenging, especially if the number of patients exceeds the availability of resources and in the absence of national guidelines to help physicians in charge. As dramatic illustration, a recent methanol poisoning outbreak in the northeast state of Assam in India has killed at least 154 people and left more than 200 people hospitalized after drinking an unregulated moonshine, known locally as "country-made liquor"[11]. Here, we report the outcome of a collective methanol intoxication that occurred in Cairo, Egypt in 2018 and discuss the different challenging issues from a public health perspective.

CASE PRESENTATION

Five Ukrainian males were referred to our emergency department in Cairo, Egypt on May 28, 2018. The patients were transferred by ambulance and accompanied by an Arabic translator. Two patients were comatose, and three others drowsy with vomiting and headaches. Detailed history was taken from the conscious persons. All five patients were recently assigned to a local multinational factory in a neighboring area and lived there together in the same building. The day before, they tried to buy alcoholic beverages but did not know any local store. So, they prepared and ingested a homemade alcoholic beverage using bottles containing 70% ethanol disinfectant bought from a local pharmacy and fresh orange juice. They drank several glasses of this beverage during the day prior. Another sixth patient drank with them but refused to come to the hospital as he felt well. We requested from the translator to convince him to come as soon as possible. He came on the next day while presenting severe impairment in visual acuity, with perception limited to hand motion for the right eye and light for the left eye. All patients were promptly admitted to the intensive care unit (ICU). Vital signs, physical and biological parameters on admission as well as management and outcome data are presented in Table 1.

FINAL DIAGNOSIS

Based on history and presence of metabolic acidosis and visual impairment in all patients, methanol poisoning was suspected.

Table 1 Clinical, biological, management and outcome data in six methanol-poisoned patients during an outbreak in Egypt

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Clinical parameters on admission						
Age in yr	41	47	41	46	42	42
Glasgow coma score	3	3	15	15	15	15
Respiratory rate as /min	32	30	26	29	23	18
Systolic/diastolic blood pressure in mmHg	80/60	60/40	110/70	110/80	100/80	150/100
Pupils	Dilated	Dilated	Dilated	Dilated	Dilated	Dilated
Repeated seizures	+	+	-	-	-	-
Ophthalmological examination	-	Diminished visual acuity bilaterally with diminished visual field for follow-up	Diminished visual acuity bilaterally for follow-up	Diminished visual acuity bilaterally for follow-up	Diminished visual acuity bilaterally for follow-up	Hand motion by the right eye and light perception by the left eye
Opthalmoscopy	Bilateral hyperemic swollen optic discs with flame-shaped shadow along superior arcade	Bilateral hyperemic optic discs with pale vassal rim	Bilateral hyperemic optic discs with peripapillary nerve fiber layer edema	Bilateral mild disc pallor and retinal edema	Bilateral pale swollen optic discs with superior and inferior retinal nerve fiber layer swelling	Bilateral disc pallor with normal retina
Biological parameters on admission						
Arterial pH	6.80	6.80	7.18	7.03	7.07	7.36
HCO_3^- concentration in mmol/L	4.2	4.5	9.7	8.2	4.3	20.9
$PaCO_2$ in mmHg	27	22	26	31	15	37
Serum creatinine in mg/dL	1.1	1.6	4.1	1.0	0.9	1.1
Blood urea nitrogen in mg/dL	26	44	26	26	31	36
AST/ALT	80/60	31/15	36/38	43/57	28/20	28/24
Hemoglobin in g/dL	15.0	15.0	13.2	15.0	15.6	14.0
Platelets in G/L	150	250	226	202	314	150
White blood cells in G/L	8.1	22.7	13.6	8.3	14.3	6.1
Management						
Sodium bicarbonates	+	+	+	+	+	+
Thiamin at 400 mg/d, IV	+	+	+	+	+	+

Leucovorin at 200 mg/d, IV	+	+	+	+	+	+
Methylprednisolone at 400 mg/d, IV	+	+	-	-	+	+
Diazepam at 30 mg/d, IV	+	+	-	-	-	-
Hemodialysis 2-h session	One session	One session /d during 4 d	One session /d during 2 d	One session	One session	One session /d during 2 d
Mechanical ventilation	+	+	-	-	-	-
Vasopressor, norepinephrine	+	-	-	-	-	-
Outcome						
Outcome	Multiorgan failure and death	Disorientation, abnormal behavior, Diminished visual acuity	Full orientation, Pneumonia, Diminished visual acuity	Full orientation, Diminished visual acuity	Full orientation, Diminished visual acuity	Full orientation, Blindness
ICU discharge	Day 1	Day 7	Day 3	Day 3	Day 3	Day 5
Risk score, predicted risk of death[1]	Risk E, 83%	Risk D, 50%	Risk A, 5%	Risk A, 5%	Risk A, 5%	Risk A, 5%

[1]Based on the risk assessment chart for the evaluation of outcome using admission parameters including coma onset, arterial pH and $PaCO_2$, according to Paasma *et al*[29].

TREATMENT

Due to the lack of readily available antidote and blood ethanol measurement in our laboratory, patients were treated with supportive care, vitamins (thiamin and leucoverin) and intermittent dialysis. Two hemodialysis devices were available in the ICU. Thus, 2-h sessions were successively provided to all patients starting with the most severely injured ones (Patient 1 to 5 then Patient 6 when admitted) and secondarily repeated on a daily basis if required by the metabolic disturbances.

OUTCOME AND FOLLOW-UP

One patient rapidly died from multiorgan failure a few hours after ICU admission. Due to persistent disorientation, brain magnetic resonance imaging was performed in Patient 2 showing bilateral, symmetrical sizable patchy areas of abnormal signals at cerebellar hemispheres and basal ganglia as well as bilateral and mainly subcortical frontal, parietal and occipital regions. Brain injuries elicited faintly bright to intermediate T2 and more bright fluid attenuation inversion recovery signals with restricted diffusion in diffusion-weighted imaging. The five survivors were discharged upon their request when possible to continue treatment and follow-up in their

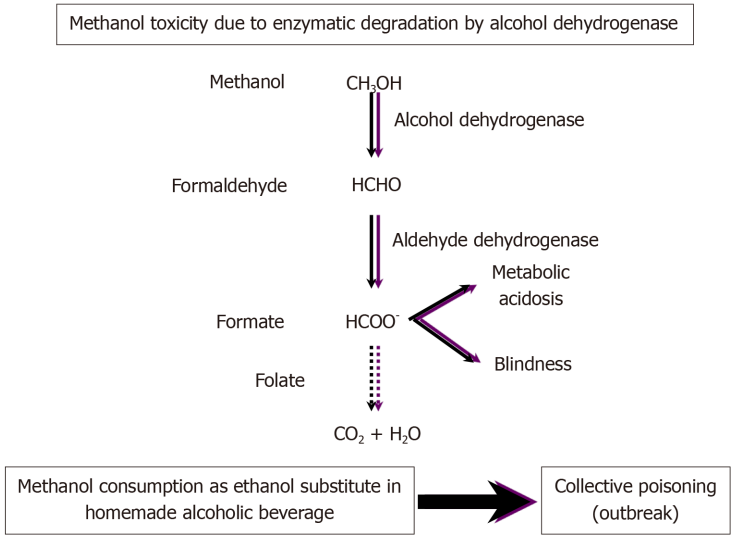

Figure 1 Metabolism pathway of methanol and its resulting toxicity in humans.

country. Before living our ICU, they gave their consent for the anonymous use of their data for research purposes.

DISCUSSION

Outbreaks of methanol poisoning occur frequently on a global basis and affect vulnerable populations[5]. The situation in Egypt is poorly known, likely with many cases and even outbreaks going unnoticed. Here, we described the features and outcome of six methanol-poisoned patients managed in Cairo, allowing us to acknowledge the limitations that influenced our therapeutic strategy and to review the main underlying public health issues that remain unsolved to date.

All six patients presented with severe metabolic acidosis, which is the most common disturbance in methanol intoxication due to the accumulation of formic acid[1,12]. All patients presented with visual disturbances, which is the only specific symptom of methanol poisoning. Visual disturbances are frequently reported in methanol poisoning, with approximately 30%-60% prevalence on hospital admission[9,13-17]. Ocular changes consist in bilateral retinal edema, hyperemia of the discs and blurring of the disc margins. Usually, optic atrophy is a late complication of methanol poisoning[12,13]. In our series, 1 patient developed almost complete blindness, probably due to his delayed admission and treatment in comparison to the others.

When methanol poisoning is suspected based on medical history, osmolal gap or anion gap metabolic acidosis, confirmation should be rapidly obtained with the measurement of blood methanol concentration[18,19]. However, if not readily available, osmolal gap has been reported to be a useful indicator for the presence of toxic alcohol to guide the treatment[19]. In our hospital, due to deficient regional resources, neither osmolality testing, anion gap measurement nor methanol leveling was readily available. Therefore, empirical therapy was immediately started based on the typical features attributed to methanol toxicity.

The full correction of metabolic acidosis and the rapid formate formation blockage and elimination are the cornerstones of management[2,12,20]. Ethanol, a competitive ADH substrate and fomepizole, a potent ADH inhibitor, are the two recommended antidotes with established effectiveness to reverse methanol toxicity[1,12,14,15,21]. Hemodialysis is effective to reverse rapidly metabolic acidosis and enhance methanol and formate elimination[2,12,20]. Leucoverin (folinic acid) is commonly administered due to its attributed effects to enhance formate metabolism in the monkey[22]. Our patients did not receive any antidote and were only treated with hemodialysis, folinic acid and supportive care. Fomepizole is not marketed in Egypt. Ethanol is not readily available at the bedside in our region; additionally, due to the non-availability of blood ethanol concentration measurement, its administration was estimated to be unsafe by the physicians in charge.

The recommended indications for extracorporeal treatment of methanol poisoning

were revisited by the international Extracorporeal Treatment in Poisoning Work Group[20]. Recommendations included any of the following criteria being attributed to methanol: Coma, seizures, new vision deficits, metabolic acidosis with blood pH ≤ 7.15, persistent metabolic acidosis despite adequate supportive measures and antidotes and serum anion gap ≥ 24 mmol/L. Intermittent hemodialysis was recognized as the modality of choice, while continuous modalities were considered as acceptable alternatives. In our series, all patients presented at least one of these criteria and were therefore dialyzed. If available, serum methanol concentration should also be considered to indicate hemodialysis if ≥ 700 mg/L (21.8 mmol/L) in the context of fomepizole therapy; if ≥ 600 mg/L (18.7 mmol/L) in the context of ethanol treatment; and if ≥ 500 mg/L (15.6 mmol/L) in the absence of an ADH blocker[20]. In the absence of methanol concentration, the osmolal gap was estimated to inform the decision. In our situation, none of these biological parameters was available, and hemodialysis decision was undertaken based on the severity of acidosis and the presence of visual impairments on admission.

Although hemodialysis should be done in severely methanol-intoxicated patients, it may be readily unavailable in case of outbreak due to limited resources[23,24]. Selection of patients to perform hemodialysis should thus be prioritized on clinical indications (respiratory, neurological or visual symptoms or reduced kidney function) rather than on absolute methanol levels[12,20]. Contrary to conventional teaching, acidosis may occur only a few hours after ingestion, but this delay is prolonged in case of ethanol co-ingestion[23]. Here, the exact starting time and duration of drinking as well as the beverage composition remained unknown. Published data are insufficient to apply 200 mg/L (6.2 mmol/L) as treatment threshold in a non-acidotic patient arriving early for care. It is possible to offer prolonged ADH inhibition with fomepizole until hemodialysis can be performed, if necessary. Nevertheless, this approach should be balanced against the longer (approximately 52 h) methanol half-life with the antidote and need for extended hospitalization[14,21,25]. In patients without significant acidosis or ocular symptoms, treatment with ADH inhibition alone has been shown to be safe and is therefore a viable option if hemodialysis is not possible or methanol concentrations are not markedly elevated.

These international recommendations should reduce the allocation of resources to patients with less severe poisoning, so that extracorporeal treatments can be prioritized to those with greater need. Guidance on risk stratification of patients with severe methanol poisoning may be useful to help physicians in charge of mass casualty care[24]. Very recently, consensus statements were established on the approach to patients in a methanol poisoning outbreak, setting up international recommendations and a triage system that identifies patients most likely to benefit, so that they are prioritized in favor of those in whom treatment is futile or those with low toxicity exposures at that time[23]. A risk assessment score utilizing simple readily available parameters on patient admission exists, and it is based on a multicenter study that included observational data from several methanol poisoning outbreaks to help identify the patients associated with poor outcome (Table 2)[26]. Low pH (pH < 7.00), coma (Glasgow coma score < 8) and inadequate hyperventilation [$PaCO_2$ ≥ 3.1 kPa (or 23 mmHg) in spite of arterial pH < 7.00] on admission were shown to be the strongest predictors of poor outcome after methanol poisoning. Interestingly, improved clinical outcome was more recently shown to be positively associated with out-of-hospital ethanol administration[27,28]. Therefore, conscious adults with suspected poisoning should be considered for administration of out-of-hospital ethanol to reduce morbidity and mortality. However, we acknowledge that such a recommendation has serious limitations in a Muslim country like Egypt.

Outcome of methanol-induced blindness appears less predictable. However, improvement of optic nerve conductivity has been reported in more than 80% of the patients during the first years of follow-up[28]. Visual disturbances on admission and coma are significantly more prevalent in the patients with visual sequelae[16]. Although depth of acidosis at presentation is the strongest determinant of the final visual acuity, no other parameter at presentation including demographics, elapsed time to presentation, symptoms, neurological examination, arterial blood gas and brain computed tomography-scan findings was found able to identify transient *versus* permanent visual injuries in the initial disturbances[17,29]. In the recent Czech mass methanol outbreak, no association was found between visual sequelae and type of antidote administered, mode of hemodialysis or folate substitution, while only pre-hospital administration of ethanol seemed beneficial, if based on the follow-up evaluating the retinal nerve fibers layer by optical coherence tomography[16]. Intravenous high-dose methylprednisolone, alone[13] or in combination with intravenous erythropoietin[30], has been suggested to reverse methanol-induced ocular

Table 2 Risk assessment for the rapid evaluation of outcome based on admission parameters, adapted from Paasma *et al*[29]

Risk group	Coma	Arterial pH	$PaCO_2$	Death risk
A	No	≥ 7.00	-	5%
B	No	6.74-6.99	-	10%
C	No	< 6.74	-	25%
D	Yes	6.74-6.99	< 3.07	50%
E	Yes	6.74-6.99	≥ 3.07	83%
F	Yes	< 6.74	-	89%

Determination of the risk group of 1 patient on admission requires the combination of all conditions for the three parameters.

injuries provided the interval between methanol consumption and starting treatment is short like in our patients; but its definitive effectiveness remains to be proved.

One major issue in mass methanol poisoning is the rapid identification of the involved causative agent. Here, our investigations concluded that the suspected beverage was homemade with alcoholic disinfectant used for medicinal purposes and sold in most of local pharmacies, in bottles lacking pamphlet and use instructions. Data on the bottles written in Arabic only showed that they contained 70% ethanol and have to be kept away from children (Figure 2). It is probable that the absence of adequate information on the disinfectant bottles was misleading and confusing.

Prevention is also a major critical issue from a public health perspective and includes public education, constraining the public purchase of methanol-containing items and storing these items securely[7]. According to the Classification, Labeling and Packaging article 17 of the European Chemical Agency's guidance of labeling and packaging, a substance and mixture classified as hazardous must bear a label including the following elements: (1) Name, address and telephone number of the supplier(s); (2) The nominal quantity of the substance or mixture in the package made available to the general public, unless this quantity is specified elsewhere on the package; and (3) Product identifiers; hazard pictograms, where applicable; the relevant signal word, where applicable; hazard statements, where applicable; and appropriate precautionary statements where applicable[31]. In addition, according to the Egyptian New Consumer Law 181/2018, the producer or supplier of any commodity must inform the consumer of all essential data about the product, including particularly its source, price, characteristics and all basic components in accordance with the Egyptian or international specifications standards. Clearly, the basic laws have not been respected in this situation.

This experience has alarmed us about the terrible consequences of shortages in staff, testing and treatment availability (antidote and extracorporeal treatments) in Egypt that may become challenging in a larger methanol poisoning outbreak. Poor knowledge of management of methanol poisoning among health workers and late diagnosis of the suspected cases may result in high case fatality. Increasing local competencies is crucial since mobilization of international teams in case of major outbreaks takes time[5]. A strategic plan should be in place in the rare event of an outbreak. Government health authorities should search for poisoned individuals who have not yet presented to hospitals. Joint effort between local health authorities and non-governmental organizations with the necessary infrastructure and emergency experience combined with provision of detailed and locally adapted treatment protocols and training is life-saving. Guidelines have to be rapidly disseminated by email alert systems or other internet-based services or hand-delivered when required in resource-limited regions.

CONCLUSION

Mass methanol poisoning with unpredictable risk assessment represents a major threat in developing countries with resource limitations like Egypt. In this local outbreak, immediate supply of supportive care and hemodialysis overcame the deficit in diagnostic testing and antidotes. This study brings attention to the risks due to sold products with no warnings or ingredients notice. Like the ongoing extended methanol

Figure 2 Label of the locally produced disinfectant sold in the Egyptian pharmacies.

poisoning outbreak in India, dramatic consequences are not impossible to exclude.

ACKNOWLEDGMENTS

The authors would like to acknowledge Alison Good, Scotland, United Kingdom, for her helpful review of this manuscript.

REFERENCES

1 **Kraut JA**, Mullins ME. Toxic Alcohols. *N Engl J Med* 2018; **378**: 270-280 [PMID: 29342392 DOI: 10.1056/NEJMra1615295]
2 **Mégarbane B**, Borron SW, Baud FJ. Current recommendations for treatment of severe toxic alcohol poisonings. *Intensive Care Med* 2005; **31**: 189-195 [PMID: 15627163 DOI: 10.1007/s00134-004-2521-0]
3 **Aghababaeian H**, Araghi Ahvazi L, Ostadtaghizadeh A. The Methanol Poisoning Outbreaks in Iran 2018. *Alcohol Alcohol* 2019; **54**: 128-130 [PMID: 30715164 DOI: 10.1093/alcalc/agz005]
4 **Onyekwere N**, Nwadiuto I, Maleghemi S, Maduka O, Numbere TW, Akpuh N, Kanu E, Katchy I, Okeafor I. Methanol poisoning in South- South Nigeria: Reflections on the outbreak response. *J Public Health Afr* 2018; **9**: 748 [PMID: 30079165 DOI: 10.4081/jphia.2018.748]
5 **Rostrup M**, Edwards JK, Abukalish M, Ezzabi M, Some D, Ritter H, Menge T, Abdelrahman A, Rootwelt R, Janssens B, Lind K, Paasma R, Hovda KE. The Methanol Poisoning Outbreaks in Libya 2013 and Kenya 2014. *PLoS One* 2016; **11**: e0152676 [PMID: 27030969 DOI: 10.1371/journal.pone.0152676]
6 **Hassanian-Moghaddam H**, Nikfarjam A, Mirafzal A, Saberinia A, Nasehi AA, Masoumi Asl H, Memaryan N. Methanol mass poisoning in Iran: role of case finding in outbreak management. *J Public Health (Oxf)* 2015; **37**: 354-359 [PMID: 24944254 DOI: 10.1093/pubmed/fdu038]
7 **Collister D**, Duff G, Palatnick W, Komenda P, Tangri N, Hingwala J. A Methanol Intoxication Outbreak From Recreational Ingestion of Fracking Fluid. *Am J Kidney Dis* 2017; **69**: 696-700 [PMID: 28111025 DOI: 10.1053/j.ajkd.2016.10.029]
8 **Zakharov S**, Pelclova D, Urban P, Navratil T, Diblik P, Kuthan P, Hubacek JA, Miovsky M, Klempir J, Vaneckova M, Seidl Z, Pilin A, Fenclova Z, Petrik V, Kotikova K, Nurieva O, Ridzon P, Rulisek J, Komarc M, Hovda KE. Czech mass methanol outbreak 2012: epidemiology, challenges and clinical features. *Clin Toxicol (Phila)* 2014; **52**: 1013-1024 [PMID: 25345388 DOI: 10.3109/15563650.2014.974106]
9 **Paasma R**, Hovda KE, Tikkerberi A, Jacobsen D. Methanol mass poisoning in Estonia: outbreak in 154 patients. *Clin Toxicol (Phila)* 2007; **45**: 152-157 [PMID: 17364632 DOI: 10.1080/15563650600956329]
10 **Hovda KE**, Hunderi OH, Tafjord AB, Dunlop O, Rudberg N, Jacobsen D. Methanol outbreak in Norway 2002-2004: epidemiology, clinical features and prognostic signs. *J Intern Med* 2005; **258**: 181-190 [PMID: 16018795 DOI: 10.1111/j.1365-2796.2005.01521.x]
11 **Gupta S**, Guy J, Humayun H, CNN. Toxic moonshine kills 154 people and leaves hundreds hospitalized in India. [published 25 February 2019]. Available from: https://edition.cnn.com/2019/02/24/asia/india-alcohol-poisoning/index.html
12 **Barceloux DG**, Bond GR, Krenzelok EP, Cooper H, Vale JA; American Academy of Clinical Toxicology Ad Hoc Committee on the Treatment Guidelines for Methanol Poisoning. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. *J Toxicol Clin Toxicol* 2002; **40**: 415-446 [PMID: 12216995 DOI: 10.1081/clt-120006745]
13 **Sodhi PK**, Goyal JL, Mehta DK. Methanol-induced optic neuropathy: treatment with intravenous high dose steroids. *Int J Clin Pract* 2001; **55**: 599-602 [PMID: 11770356 DOI: 10.2169/internalmedicine.40.1162]
14 **Mégarbane B**, Borron SW, Trout H, Hantson P, Jaeger A, Krencker E, Bismuth C, Baud FJ. Treatment of acute methanol poisoning with fomepizole. *Intensive Care Med* 2001; **27**: 1370-1378 [PMID: 11511951 DOI: 10.1007/s001340101011]
15 **Brent J**, McMartin K, Phillips S, Aaron C, Kulig K; Methylpyrazole for Toxic Alcohols Study Group. Fomepizole for the treatment of methanol poisoning. *N Engl J Med* 2001; **344**: 424-429 [PMID: 11172179

DOI: 10.1056/NEJM200102083440605]
16 **Zakharov S**, Pelclova D, Diblik P, Urban P, Kuthan P, Nurieva O, Kotikova K, Navratil T, Komarc M, Belacek J, Seidl Z, Vaneckova M, Hubacek JA, Bezdicek O, Klempir J, Yurchenko M, Ruzicka E, Miovsky M, Janikova B, Hovda KE. Long-term visual damage after acute methanol poisonings: Longitudinal cross-sectional study in 50 patients. *Clin Toxicol (Phila)* 2015; **53**: 884-892 [PMID: 26364866 DOI: 10.3109/15563650.2015.1086488]
17 **Desai T**, Sudhalkar A, Vyas U, Khamar B. Methanol poisoning: predictors of visual outcomes. *JAMA Ophthalmol* 2013; **131**: 358-364 [PMID: 23303293 DOI: 10.1001/jamaophthalmol.2013.1463]
18 **Kraut JA**. Diagnosis of toxic alcohols: limitations of present methods. *Clin Toxicol (Phila)* 2015; **53**: 589-595 [PMID: 26114345 DOI: 10.3109/15563650.2015.1056880]
19 **Hovda KE**, Hunderi OH, Rudberg N, Froyshov S, Jacobsen D. Anion and osmolal gaps in the diagnosis of methanol poisoning: clinical study in 28 patients. *Intensive Care Med* 2004; **30**: 1842-1846 [PMID: 15241587 DOI: 10.1007/s00134-004-2373-7]
20 **Roberts DM**, Yates C, Megarbane B, Winchester JF, Maclaren R, Gosselin S, Nolin TD, Lavergne V, Hoffman RS, Ghannoum M; EXTRIP Work Group. Recommendations for the role of extracorporeal treatments in the management of acute methanol poisoning: a systematic review and consensus statement. *Crit Care Med* 2015; **43**: 461-472 [PMID: 25493973 DOI: 10.1097/CCM.0000000000000708]
21 **Brent J**. Fomepizole for ethylene glycol and methanol poisoning. *N Engl J Med* 2009; **360**: 2216-2223 [PMID: 19458366 DOI: 10.1056/NEJMct0806112]
22 **McMartin KE**, Martin-Amat G, Makar AB, Tephly TR. Methanol poisoning. V. Role of formate metabolism in the monkey. *J Pharmacol Exp Ther* 1977; **201**: 564-572 [PMID: 405471 DOI: 10.1111/j.1749-6632.1986.tb23619.x]
23 **Hassanian-Moghaddam H**, Zamani N, Roberts DM, Brent J, McMartin K, Aaron C, Eddleston M, Dargan PI, Olson K, Nelson L, Bhalla A, Hantson P, Jacobsen D, Megarbane B, Balali-Mood M, Buckley NA, Zakharov S, Paasma R, Jarwani B, Mirafzal A, Salek T, Hovda KE. Consensus statements on the approach to patients in a methanol poisoning outbreak. *Clin Toxicol (Phila)* 2019; **57**: 1129-1136 [PMID: 31328583 DOI: 10.1080/15563650.2019.1636992]
24 **Roberts DM**, Hoffman RS, Gosselin S, Megarbane B, Yates C, Ghannoum M. The authors reply. *Crit Care Med* 2015; **43**: e211-e212 [PMID: 25978175 DOI: 10.1097/CCM.0000000000001006]
25 **Hovda KE**, Jacobsen D. Expert opinion: fomepizole may ameliorate the need for hemodialysis in methanol poisoning. *Hum Exp Toxicol* 2008; **27**: 539-546 [PMID: 18829729 DOI: 10.1177/0960327108095992]
26 **Sanaei-Zadeh H**, Zamani N, Shadnia S. Outcomes of visual disturbances after methanol poisoning. *Clin Toxicol (Phila)* 2011; **49**: 102-107 [PMID: 21370946 DOI: 10.3109/15563650.2011.556642]
27 **Zakharov S**, Pelclova D, Urban P, Navratil T, Nurieva O, Kotikova K, Diblik P, Kurcova I, Belacek J, Komarc M, Eddleston M, Hovda KE. Use of Out-of-Hospital Ethanol Administration to Improve Outcome in Mass Methanol Outbreaks. *Ann Emerg Med* 2016; **68**: 52-61 [PMID: 26875060 DOI: 10.1016/j.annemergmed.2016.01.010]
28 **Nurieva O**, Hubacek JA, Urban P, Hlusicka J, Diblik P, Kuthan P, Sklenka P, Meliska M, Bydzovsky J, Heissigerova J, Kotikova K, Navratil T, Komarc M, Seidl Z, Vaneckova M, Vojtova L, Zakharov S. Clinical and genetic determinants of chronic visual pathway changes after methanol - induced optic neuropathy: four-year follow-up study. *Clin Toxicol (Phila)* 2019; **57**: 387-397 [PMID: 30451020 DOI: 10.1080/15563650.2018.1532083]
29 **Paasma R**, Hovda KE, Hassanian-Moghaddam H, Brahmi N, Afshari R, Sandvik L, Jacobsen D. Risk factors related to poor outcome after methanol poisoning and the relation between outcome and antidotes--a multicenter study. *Clin Toxicol (Phila)* 2012; **50**: 823-831 [PMID: 22992104 DOI: 10.3109/15563650.2012.728224]
30 **Pakdel F**, Sanjari MS, Naderi A, Pirmarzdashti N, Haghighi A, Kashkouli MB. Erythropoietin in Treatment of Methanol Optic Neuropathy. *J Neuroophthalmol* 2018; **38**: 167-171 [PMID: 29300238 DOI: 10.1097/WNO.0000000000000614]
31 European Chemical Agency's guidance of labeling and packaging. [cited 6 April 2020]. Available from: https://echa.europa.eu/documents/10162/23036412/clp_labelling_en.pdf/89628d94-573a-4024-86cc-0b4052a74d65

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 2220-3141 (online)

World Journal of

Critical Care Medicine

World J Crit Care Med 2020 October 18; 9(4): 63-73

Published by Baishideng Publishing Group Inc

WJCCM

World Journal of Critical Care Medicine

Contents

Irregular Volume 9 Number 4 October 18, 2020

ORIGINAL ARTICLE

Case Control Study

World Journal of Critical Care Medicine

Irregular Volume 9 Number 4 October 18, 2020

Contents

ABOUT COVER

Editorial board member of *World Journal of Critical Care Medicine*, Dr. Hossein Hassanian-Moghaddam is an Associate Professor at the Shahid Beheshti University of Medical Sciences (Tehran, Iran). Having received his MD degree from Mashhad University of Medical Sciences in 1993, he has since conducted his clinical practice in Loghman Hakim Hospital, the largest university-affiliated poison center in the world, with almost 24000 emergency-presenting poisoned patients and housing specialized toxicological ICUs and wards. His research interests include opioids, toxic alcohols, stimulants, pesticides and pharmaceutical poisoning, which are reflected in his more than 200 published abstracts/articles in peer-reviewed scientific journals and international congresses. Currently, he serves as Chair of the Scientific Committee of the Asia Pacific Association of Medical Toxicology. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of the *World Journal of Critical Care Medicine* (*WJCCM*, *World J Crit Care Med*) is to provide scholars and readers from various fields of critical care medicine with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCCM mainly publishes articles reporting research results and findings obtained in the field of critical care medicine and covering a wide range of topics including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, ICU management and treatment control, sedation and analgesia, severe infection, *etc*.

INDEXING/ABSTRACTING

The *WJCCM* is now indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Irregular

EDITORS-IN-CHIEF
KLE Hon

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

PUBLICATION DATE
October 18, 2020

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2020 October 18; 9(4): 63-73

DOI: 10.5492/wjccm.v9.i4.63

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Case Control Study

Association between thrombomodulin and high mobility group box 1 in sepsis patients

Adriana Teixeira Rodrigues, Julia Teixeira Rodrigues, Carolina Teixeira Rodrigues, Caroline Maria de Oliveira Volpe, Fabiana Rocha-Silva, Jose Augusto Nogueira-Machado, Luiz Ronaldo Alberti

ORCID number: Adriana Teixeira Rodrigues 0000-0002-1735-5073; Julia Teixeira Rodrigues 0000-0001-7309-5926,; Carolina Teixeira Rodrigues 0000-0002-3086-2846; Caroline Maria de Oliveira Volpe 0000-0003-0791-8538; Fabiana Rocha-Silva 000-0003-2698-9649; Jose Augusto Nogueira-Machado 0000-0002-8257-6585; Luiz Ronaldo Alberti 0000-0002-5229-3971.

Author contributions: Rodrigues AT analyzed the data and wrote the manuscript; Rodrigues AT, Volpe CMO, Rocha-Silva F, Nogueira-Machado JA and Alberti LR designed the research study and corrected the manuscript; Rodrigues JT and Rodrigues CT participated to the collection of the human material (blood sample), data and corrected the manuscript; all authors have read and approve the final manuscript.

Institutional review board statement: The study and the Free and Informed Consent (FIC) form, signed by the patients or their representatives, were approved by the Institutional Review Board (IRB) of the Santa Casa Hospital - Education and Research, Belo Horizonte, Brazil, under No. 2778641, on July 20, 2018.

Informed consent statement:

Adriana Teixeira Rodrigues, Department of Pediatrics, School of Medicine, Federal University of Minas Gerais, Belo Horizonte 30130-100, Minas Gerais, Brazil

Adriana Teixeira Rodrigues, Luiz Ronaldo Alberti, Graduation Program in Medicine/Biomedicine - Santa Casa Hospital - Education and Research, Belo Horizonte 30150-240, Minas Gerais, Brazil

Julia Teixeira Rodrigues, Department of Pharmacy, Federal University of Minas Gerais, Belo Horizonte 31270-901, Minas Gerais, Brazil

Carolina Teixeira Rodrigues, Department of Internal Medicine, Unimed Hospital, Belo Horizonte 30150-340, Minas Gerais, Brazil

Caroline Maria de Oliveira Volpe, Jose Augusto Nogueira-Machado, Department of Immunology, Graduation Program in Medicine/Biomedicine - Santa Casa Hospital - Education and Research, Belo Horizonte 30150-240, Minas Gerais, Brazil

Fabiana Rocha-Silva, Clinical Laboratory, Graduation Program in Medicine/Biomedicine - Santa Casa Hospital - Education and Research, Belo Horizonte 30150-240, Minas Gerais, Brazil

Luiz Ronaldo Alberti, Department of Surgery, School of Medicine, Federal University of Minas Gerais, Belo Horizonte 30220-000, Minas Gerais, Brazil

Corresponding author: Adriana Teixeira Rodrigues, MD, PhD, Assistant Professor, Attending Doctor, Department of Pediatrics, School of Medicine, Federal University of Minas Gerais, 190 Alfredo Balena Avenue, Belo Horizonte 30130-100, Minas Gerais, Brazil.
adrianatr92@gmail.com

Abstract

BACKGROUND

High mobility group box 1 (HMGB1) has been studied as a molecule associated with severe outcomes in sepsis and thrombomodulin (TM) seems to decrease HMGB1 activity.

AIM

To investigate the role of the thrombomodulin/high mobility group box 1 (T/H)

Informed written consent was obtained from the patient for publication of this manuscript.

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at adrianatr92@gmail.com. Participants gave informed consent for data sharing.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Manuscript source: Unsolicited manuscript

Received: June 16, 2020
Peer-review started: June 16, 2020
First decision: July 21, 2020
Revised: July 31, 2020
Accepted: August 24, 2020
Article in press: August 24, 2020
Published online: October 18, 2020

P-Reviewer: Pota V
S-Editor: Yan JP
L-Editor: A
P-Editor: Li JH

ratio in patients with sepsis and their association with their clinic, testing the hypothesis that higher ratios are associated with better outcomes.

METHODS
Twenty patients diagnosed with sepsis or septic shock, according to the 2016 criteria sepsis and septic shock (Sepsis-3), were studied. Patients were followed until they left the intensive care unit or until they achieved 28 d of hospitalization (D28). The following clinical outcomes were observed: Sequential Organ Failure Assessment (SOFA) score; Need for mechanical pulmonary ventilation; Presence of septic shock; Occurrence of sepsis-induced coagulopathy; Need for renal replacement therapy (RRT); and Death.

RESULTS
The results showed that patients with SOFA scores greater than or equal to 12 points had higher serum levels of TM: 76.41 ± 29.21 pg/mL *vs* 37.41 ± 22.55 pg/mL among those whose SOFA scores were less than 12 points, $P = 0.003$. The T/H ratio was also higher in patients whose SOFA scores were greater than or equal to 12 points, $P = 0.001$. The T/H ratio was, on average, three times higher in patients in need of RRT (0.38 ± 0.14 *vs* 0.11 ± 0.09), $P < 0.001$.

CONCLUSION
Higher serum levels of TM and, therefore, higher T/H ratio in the first 24 h after the diagnosis of sepsis were associated with more severe disease and the need for renal replacement therapy, while those with better clinical outcomes and those who were discharged before D28 showed a tendency for lower T/H ratio values.

Key Words: High mobility group box 1; Sepsis; Thrombomodulin; Renal replacement therapy; Mechanical ventilation; Septic shock

Core Tip: The knowledge of physiological mechanisms that lead an organism to respond to an infectious agent with such intensity is of great importance. It has been described that during sepsis, an organism produces intense inflammatory activity, caused by the action of several inflammatory mediators. High mobility group box 1 (HMGB1) has been the target of recent studies for its proinflammatory actions as well as for the possibility of having its action reduced by thrombomodulin. For this reason, this study proposed to evaluate the relationship between thrombomodulin and HMGB1 in the initial phase of sepsis and its association with clinical outcomes in sepsis patients.

Citation: Rodrigues AT, Rodrigues JT, Rodrigues CT, Volpe CMO, Rocha-Silva F, Nogueira-Machado JA, Alberti LR. Association between thrombomodulin and high mobility group box 1 in sepsis patients. *World J Crit Care Med* 2020; 9(4): 63-73
URL: https://www.wjgnet.com/2220-3141/full/v9/i4/63.htm
DOI: https://dx.doi.org/10.5492/wjccm.v9.i4.63

INTRODUCTION

Background

Sepsis is a severe syndrome characterized by physiological, pathological and biochemical life-threatening modifications induced by an infection. It is one of the major causes of mortality in intensive care unit (ICU) worldwide. Its treatment is complex and demands the proper use of specific antibiotics, vasoactive amines, and, in certain situations, corticosteroids. In addition, advanced technology, such as mechanical pulmonary ventilators and renal replacement therapy (RRT), can also be required[1-4].

It is known that inflammatory activity is the most evident feature of sepsis and because of that the host immune response has been studied to develop new therapeutic strategies. One potential treatment relied on the modulation of pro-inflammatory mediators, such as tumor necrose factor-α (TNF-α) and interleukin-1

(IL-1). However, even though this strategy had promising results in animal models, the same results could not be replicated in human studies[5,6].

High mobility group box 1 (HMGB1) is a nuclear protein, released by cells during oxidative stress that has proinflammatory activity. It has been studied as a promising therapeutic target because of its delayed increase 12 to 18 h after TNF-α peaks[6-10]. Janeway *et al*[11], in 1989, described the role of damage-associated molecular patterns (DAMPs) during the early stages of toxemia. HMGB1 seems to act as a DAMP[6], activating macrophages and monocytes, as well as promoting dendritic cell maturation. In its reduced state, HMGB1 exhibits minimum activity. However, in sepsis, as oxidative stress increases, it assumes the role of a proinflammatory molecule and stimulates the release of some cytokines, such as IL-1β and IL-17, TNF-α, macrophage inflammatory protein (MIP)-1α, MIP-1β, MIP-2, granulocyte colony-stimulating factor and granulocyte/macrophage colony-stimulating factor[12]. HMBG1 has also been associated with a procoagulant state, promoting the occurrence of sepsis-induced coagulopathy (SIC)[13,14].

On the other hand, thrombomodulin (TM) and antithrombin (AT) seem to have immunomodulating activities in sepsis. TM is a cell membrane glycoprotein expressed on the luminal surface of endothelial cells, where it modulates thrombin procoagulant effects. Thrombin and the TM-thrombin complex can cleave HMBG1, reducing its activity and, hence, its proinflammatory action[15,16]. In animal models, the sepsis mortality rate decreases with the coadministration of AT and TM[8,16]. Xie *et al*[17] (2010) demonstrated the role of oxidative stress in animal models. They observed that the use of hydrogen gas, by reducing oxidative products, led to the decreased release of HMGB1 and proinflammatory activity. The efficacy of TM-α in the management of intravascular coagulation associated with sepsis has been evaluated in clinical trials[18], but its effects are still being evaluated.

Objectives

This study had the objective of evaluating the TM/HMGB1 ratio among sepsis cases and their associated outcomes: Sequential Organ Failure Assessment (SOFA) score; Mechanical ventilation; Shock; Coagulopathy; Severe acute kidney injury (AKI); and Death.

MATERIALS AND METHODS

Study design

This was a case-control study. Twenty patients diagnosed with sepsis or septic shock, were selected according to the 2016 criteria sepsis and septic shock (Sepsis-3) and followed until they left the ICU or until they achieved 28 d of hospitalization (D28). The following clinical outcomes were observed: SOFA score; Need for pulmonary mechanical ventilation (MV); Presence of septic shock; occurrence of SIC; Need for RRT; and Death. Their association with HMGB1 and thrombomodulin levels and thrombomodulin/high mobility group box 1 (T/H) ratio were analyzed.

Setting

This study was carried out in the ICU of Santa Casa de Belo Horizonte (SCBH) between October 2018 and March 2019.

Participants

Twenty adult patients diagnosed with sepsis (cases) were consecutively selected according to the criteria presented in 2016 by the third international consensus definitions for Sepsis-3[1]. Sepsis was confirmed by the presence of fever and/or leukocytosis or leukopenia and/or elevated C-reactive protein level associated with the presence of an infection focus and an increase in the SOFA score greater than or equal to 2 points compared to baseline scores. Sepsis patients (cases) were followed for up to 28 d in the ICU or until discharge from the unit.

The control group was formed by 20 patients without sepsis or acute severe life-threatening disease. They were invited to be included in the control group, and blood samples for the measurement of HMGB1 and TM were collected from those who had signed the informed consent form.

Laboratorial evaluation

Among the samples collected in the first 24 h of diagnosis to determine the patient

clinical state and proper patient attendance, 10 mL of blood was reserved in Vacutainer™ tubes containing saline solution to dose TM and HMGB1. The method applied for examination was sandwich ELISA. The quantification of TM and HMGB1 was performed using the ELISA kit for HMGB1 protein commercial kits, Lot: L160322647 e DOU SET® Human Thrombomodulin/BDCA-3, Catalog No. DY3947 (Lot P 168874), following the manufacturer's guidelines.

For the diagnosis and clinical management of patients with sepsis (cases), the following exams were performed and data collected, as requested by the assistant medical team: Hemogram; Determination of international normalized ratio (INR) and activated prothrombin time; Dosage of C-reactive protein, urea and creatinine as well as the arterial blood gas and lactate dosage in arterial blood; Determination of serum levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma-glutamyl-transferase; Serum bilirubin measurements; Blood cultures, urine cultures; and secretion cultures.

Analysis and comparison of clinical evaluation

The controls and cases were compared according to their demographic, clinical and laboratory characteristics and levels of HMGB1 and thrombomodulin and the T/H ratio. The association of serum levels of HMGB1 and thrombomodulin and the T/H ratio between cases and the following clinical outcomes was assessed: SOFA score greater than or equal to 12; Need for and time of pulmonary MV; PaO_2/FiO_2 ratio[19]; Presence of shock; Presence of SIC; Presence of severe AKI with the need for RRT; and Death until D28.

Variables and definitions

The clinical evaluation of the patients with sepsis was made through prospective analysis of their medical records from the time of sepsis diagnosis until their discharge from the ICU or until D28. The diagnosis of sepsis followed the third international consensus definitions for Sepsis-3 recommendations[1]. The parameters evaluated included age; sex; SOFA score greater than 12 points[20,21]; need for and duration of mechanical pulmonary ventilation; presence of septic shock (according to third international consensus definitions for Sepsis-3)[1]; presence of AKI according to the criteria established by the Kidney Disease Improving Global Outcomes Group[22,23] and need for RRT; presence of coagulation disorders, such as thrombocytopenia and elevated INR values; time in ICU therapy; and death. The score for the diagnosis of SIC score proposed by Iba *et al*[24] in 2017 and validated by Yamakawa *et al*[25] (2019) was used to define the presence of SIC. It considers three parameters: The INR, platelet count, and SOFA score.

The sepsis management protocol in the ICU of the SCBH recommends the use of low-molecular-weight heparin in patients with septic shock. Additionally, if there is a contraindication to its use, mechanical prophylaxis should be considered.

The SOFA score with scores equal to or greater than 12 points was chosen as a cohort point because it has been associated with higher mortality rates by some authors[20,21].

These outcomes were correlated with the TM and HMGB1 serum levels in the peripheral blood of patients diagnosed with sepsis (case group), testing the hypothesis that higher T/H ratios could be associated with better outcomes.

Study size

The sample size was calculated using Open Epi, open source epidemiological statistics for public health, version 3.01, updated in 2013 (available at https://www.openepi.com/SampleSize/SSPropor.htm), admitting alpha error of 0.05, beta error of 0.20 (80% statistical power). Considering the number of beds in the ICU (110 beds) and the frequency of sepsis patients in Brazilian ICUs (16.7%)[2] the sample size found was 13 patients/group. In order address potential bias an analysis of the power to compare two means was also performed using the normal comparison method considering a 95% confidence interval, 80% comparative power and sample size ratio (group2/group1).

Statistical analysis

The statistical analysis was performed using Epi Info, version 3.5.4 for Windows, Atlanta: Centers for Disease Control and Prevention[26]. The ANOVA test was used to compare parametric continuous numerical variables, and the Mann-Whitney/Wilcoxon and Kruskal-Wallis test when ANOVA was not indicated. The results were expressed as the mean ± SD, when they were parametric, or the median

and variation between the first and third quartiles, when nonparametric. The comparison of the distribution of categorical variables was analyzed through Fisher's test, two-sided Student's, *t*-tests and yates corrected chi-squared (χ^2) test. The significance of probability was considered expressive when its value was less than 0.05 ($P < 0.05$).

RESULTS

The demographic characteristics of the cases and controls are shown in Table 1. The patients demonstrated a higher average age than the controls. The control group displayed higher weight and BMI values than the patients (Table 1).

The comorbidities found more frequently among cases were heart disease; high blood pressure or heart valve disease (40%); oncologic or hematologic diseases (45%); compensated chronic liver disease (40%); post-liver transplantation (5%); non-dialysis chronic kidney disease (15%); dialysis CKD (5%); chronic obstructive pulmonary disease (10%); and diabetes mellitus (15%).

Patients diagnosed with sepsis (cases) had a mean SOFA score of 9.6 ± 4.8 points with the following average per system, as shown in Table 2. The cases that evolved to death had mean SOFA scores equal to 12.83 ± 2.64 points.

There was no significant difference between the cases and controls in terms of the global evaluation of the serum dosage of HMGB1 (291.11 ± 119.49 pg/mL *vs* 328.14 ± 164.04 pg/mL), TM (52.9 ± 31.49 pg/mL *vs* 53.31 ± 37.69 pg/mL) and the T/H ratio (0.22 ± 0.17 *vs* 0.21 ± 0.18), $P = 0.419$, 0.970 and 0.857 (*t*-test) respectively. However, when sepsis patients (case group) with SOFA scores ≥ 12 points were compared to those with SOFA scores < 12 points, there was a significant difference between those groups in terms of both the TM level and the T/H ratio (Figure 1).

Among the 20 patients with sepsis (cases), 14 of them (70%) needed MV. The mean MV time was 9.25 ± 9.8 d. Among the case group, the level of TM and HMGB1 had no association with the need of VM nor the time (d) of mechanical ventilation $P = 0.509$ and 0.888, respectively (Mann-Whitney test). The mean T/H ratio among the case group was not associated with the mean time in MV either, $P = 0.760$ (ANOVA).

Regarding hemodynamic alterations, fourteen patients in the case group (70%) required the use of vasoactive amines to maintain a mean arterial pressure (MAP) above 65 mmHg, and eleven (55%) met the septic shock criteria according to the Sepsis-3[1]. The study showed a mean TM serum level of 54.48 ± 36.34 pg/mL for those patients diagnosed with septic shock and 50.79 ± 23.97 pg/mL for those patients without septic shock, $P = 0.797$ (*t*-test) and the T/H ratio was 0.21 ± 0.17 and 0.23 ± 0.16 for those with and without shock, respectively, $P = 0.791$ (*t*-test). The HMGB1 serum levels were 313.39 pg/mL ± 119.13 pg/mL and 263.96 ± 121.26 pg/mL for those with and without shock, respectively, $P = 0.227$ (*t*-test).

Concerning coagulation disorders, a median platelet count of 177 × 10^9/L (QR 63 × 10^9/L-312 × 10^9/L) was found in patients with sepsis (cases) and of 185 × 10^9/L (QR 164 × 10^9/L-213 × 10^9/L) in the control group, $P = 0.807$ (Mann-Whitney test). Eight patients in the case group (40%) demonstrated platelets values lower than 150 × 10^9/L. The mean INR was 1.3 ± 0.43. The difference between cases with RNI ≤ 1.2 or > 1.2 is showed in Table 3.

Among the sepsis patients (case group), eight (40%) met the criteria of SIC[24] as shown in Table 4. Concerning renal function, the median serum level of creatinine was 2.5 (QR 0.87-4.19) mg/dL among the case group and 1.03 (QR 0.89-1.12) mg/dL among the control group, $P = 0.09$ (Mann-Whitney test). Twelve patients in the case group (60%) had acute kidney insufficiency secondary to sepsis, and 10 (50%) required RRT.

The presence of severe acute kidney failure with the need for RRT revealed a significant association with serum levels of TM and the T/H ratio, as shown in Table 5. The patients stayed in the ICU for an average of 15.05 ± 10.2 d. Nine (45%) were discharged from the ICU before D28, five (25%) stayed for more than 28 d, and six (30%) died. In terms of the cases' evolution (discharge, ICU stay on D28 or death), the HMGB1 levels were 305.47 ± 103.15 pg/mL, 311.5 ± 188.41 pg/mL and 252.575 ± 79.21 pg/mL respectively, $P = 0.662$, and TM: 40.78 ± 24.34 pg/mL, 55.74 ± 32.12 pg/mL and 68.96 ± 37.59 pg/mL, $P = 0.240$. Nevertheless, patients who were discharged before D28 displayed had a lower T/H ratio (0.14 ± 0.09) compared to those who died or remained hospitalized after D28 (0.28 ± 0.18), $P = 0.039$ (*t*-test).

Table 1 Demographic characteristics

	Case group (*n* = 20)	Controls (*n* = 20)	
	mean ± SD	mean ± SD	*P* value
Age (yr)	58.10 ± 16.08	39.40 ± 12.15	< 0.001[1]
Weight (kg)	58.40 ± 11.01	69.40 ± 12.50	0.005[1]
BMI (kg/m^2)	23.30 ± 2.50	26.38 ± 3.67	0.004[1]
Gender *n* (%)			0.327[2]
Women	11 (55)	14 (70)	
Men	9 (45)	6 (30)	

[1]Represent *t* test.
[2]Represent χ^2.

Table 2 Sequential Organ Failure Assessment scores among sepsis patients (cases)

System	Points ± SD
Overall mean score	9.6 ± 4.8
Respiratory function	2.1 ± 1.28
Scoring in the coagulation system	1.1 ± 1.56
Scoring in circulatory function	2.7 ± 1.63
Liver function score	0.1 ± 0.22
Neurological function	1.61 ± 0.85
Renal function	2.3 ± 1.87

Table 3 Levels of thrombomodulin, high mobility group box 1, thrombomodulin/high mobility group box 1 ratio and international normalized ratio value

	Cases (*n* = 20)		
	INR ≤ 1.2 (*n* = 13)	INR > 1.2 (*n* = 7)	*P* value[1]
HMGB1 (pg/mL)	300.28 ± 133.21	261.81 ± 133.21	0.431
TM (pg/mL)	46.67 ± 26.71	64.77 ± 38.33	0.875
T/H	0.19 ± 0.15	0.28 ± 0.18	0.257

[1]Represent *t* test. INR: International normalized ratio; HMGB1: High mobility group box 1; TM: Thrombomodulin; T/H: Thrombomodulin/high mobility group box 1.

DISCUSSION

The aim of the study was to test the hypothesis that higher T/H ratios would be associated with better outcomes, considering the anti-inflammatory activity of TM. However, the study had several limitations, including the small sample size, its observational characteristic and its being conducted in one single center.

Sepsis is currently the leading cause of death in ICUs[1,2,6,19,27,28], affecting more frequently patients with extreme ages and patients with chronic diseases[1,29]. Regarding the serum level of HMGB1, elevated values are not expected in the initial phase of sepsis. Gibot *et al*[30] (2007) demonstrated that serum HMGB1 levels greater than 4000 pg/mL (4 ng/mL) on the third evaluation day patients with septic shock were associated with a higher risk of death, with an odds ratio equal to 5.5 and ranging from 1.3-23.6 considering the 95% confidence interval. However, as occurred in the current study, the authors found no significant association between HMBG1 and the clinical and laboratory parameters that make up the SOFA score when these were

Table 4 Levels of thrombomodulin, high mobility group box 1, thrombomodulin/high mobility group box 1 ratio and the presence of sepsis-induced coagulopathy

	Cases (n = 20)		
	With SIC (n = 8)	Without SIC (n = 12)	P value[1]
HMGB1 (pg/mL)	264.04 ± 84.01	309.22 ± 138.97	0.422
TM (pg/mL)	74.78 ± 28.95	38.44 ± 24.56	0.007[2]
T/H	0.32 ± 0.16	0.16 ± 0.13	0.034[3]

[1]Represent *t* test.
[2]Power for comparing two means (PCTM) > 80%.
[3]PCTM < 80%. TM: Thrombomodulin; HMGB1: High mobility group box 1; T/H: Thrombomodulin/high mobility group box 1 ratio; SIC: Sepsis-induced coagulopathy.

Table 5 Association between levels of thrombomodulin, high mobility group box 1 and the thrombomodulin/high mobility group box 1 ratio and renal replacement therapy

	RRT (case group, n = 20)		
	Yes (n = 10)	No (n = 10)	P value[1]
HMGB1 (pg/mL)	236.00 ± 84.00	346.90 ± 130.10	0.026[2]
TM (pg/mL)	75.37 ± 27.49	34.60 ± 22.58	0.002[3]
T/H	0.38 ± 0.14	0.11 ± 0.09	< 0.001[3]

[1]Represent *t* test.
[2]Power for comparing two means (PCTM) > 80%.
[3]PCTM < 80%. TM: Thrombomodulin; HMGB1: High mobility group box 1; T/H: Thrombomodulin ratio/high mobility group box 1; RRT: Renal replacement therapy.

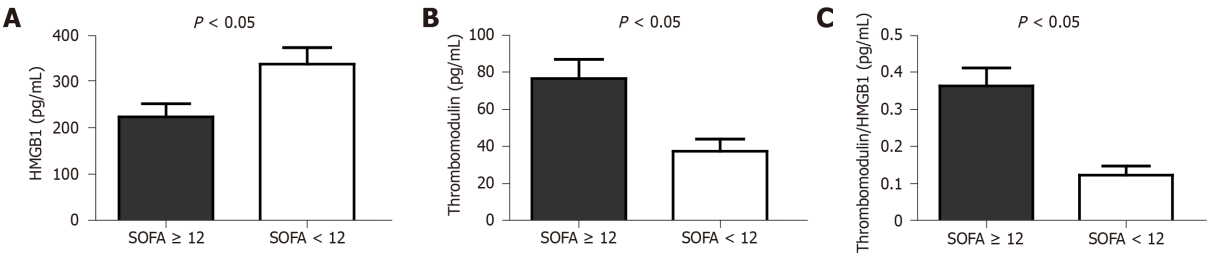

Figure 1 Levels of high mobility group box 1 (A, P = 0.034), thrombomodulin (B, [1]P = 0.003) and thrombomodulin/high mobility group box 1 ratio (C, [1]P = 0.001) in case group divided according to Sequential Organ Failure Assessment score. Values expressed in mean ± SE, unpaired Student *t* test analysis. [1]Power for comparing two means > 80%. HMGB1: High mobility group box 1; SOFA: Sequential Organ Failure Assessment.

assessed separately[30,31]. Other authors have failed to demonstrate an association between serum HMGB1 levels and patient survival in other clinical situations[32,33].

However, the aim of this study was to assess the relationship between the two molecules TM and HMGB1 in the first 24 h and their association with the evolution of patients with sepsis (cases). Some experimental studies suggest that TM is able to reduce the signaling action of HMGB1 in sepsis, and clinical trials are underway to evaluate the effect of TM administration on patients with sepsis[8,13,34].

Regarding hemodynamic conditions, two-thirds of the patients' case group needed vasoactive drugs to maintain a MAP greater than or equal to 65 mmHg. Hemodynamic changes in sepsis result from the association among complex mechanisms, both cellular and humoral, which lead to endothelial lesions, promote greater vascular permeability and, hence, cause organ damage[35]. Among humoral reactions, the cytokines released by macrophages play an important role in the inflammatory response to infection[36]. This set of responses to an offending agent can lead to the activation of the coagulation cascade and, consequently, to disseminated

intravascular coagulation with impaired tissue perfusion of organs[22,37].

The hemodynamic changes observed in patients with septic shock can also cause acute renal dysfunction, which appears as a consequence of immunological, toxic and inflammatory mechanisms that are involved in kidney damage. Fortunately, better outcomes have been observed among patients with AKI who require RRT in recent years. This change in prognosis is probably due to improvements in the sensitivity of the diagnosis of AKI, and, consequently, to the onset of RRT at a more appropriate time[22,38].

In this study, it was observed that 50% of the cases' patients required RRT. Levy *et al*[39], in 2010 reported that 85.6% of patients with sepsis had cardiovascular dysfunction, 30.8% had respiratory dysfunction, 39.5% had renal dysfunction, 10.2% had hepatic impairment, and 25.7% had hematological abnormalities. Okamoto *et al*[40], 2012, studying acute renal failure in patients with sepsis, observed that, although the presence of acute renal failure was not associated with a longer hospital stay, mortality was twice as high in septic patients with acute renal failure.

Although hemodynamic changes were not associated with changes in serum TM and HMGB1 nor T/H ratio in the present study, cases who needed RRT presented higher levels of TM in peripheral blood and higher T/H ratios when compared to controls and cases without RRT. TM is also a marker of endothelial injury, and its increase in patients with severe AKI could be secondary to higher production rates or reduced clearance by the kidney, as noted by Małyszko *et al*[41] in 2004.

Regarding sepsis coagulation disorders, there is the possibility of confounding factors such as decompensated chronic liver diseases or the use of oral anticoagulants. In the current study only one patient had chronic liver disease, but this patient had no changes in clotting factors or platelet counts. The sepsis management protocol in the ICU of the SCBH recommends the use of low-molecular-weight heparin instead of oral anticoagulants in patients with septic shock or mechanical prophylaxis when low-molecular-weight heparin is not indicated.

Activation of the coagulation system in sepsis occurs through a multifactorial mechanism and involves the activation of PRRs by PAMPs and DAMPs, including HMGB1, which has been associated with a procoagulant state and the presence of disseminated intravascular coagulation[13,14,42]. In sepsis, platelet activation can be triggered by the action of thrombin and by inflammatory mediators that promote thrombocytopenia, thrombin generation and increased inflammation[43]. Platelets are also capable of releasing HMGB1, which plays a proinflammatory and an important procoagulant role[42,44]. Another molecule whose role in SIC has been studied is TM[8,15,45]. TM and the TM-antithrombin complex assist in the degradation of HMGB1 and, therefore, reduce its proinflammatory effect[13]. Although this effect has been observed in animal models[8,15,45], in the current study, a positive association was observed between patients with higher TM levels in the first 24 h and the presence of SIC[24] compared to controls and cases without SIC.

The clinical use of recombinant TM has been tested, and although theoretically promising, it has not been associated with a significant reduction in mortality or other secondary outcomes when compared to placebo to date[2,34,46,47]. Rhodes *et al*[48] recommended not using antithrombin due to a lack of evidence of an effect. Regarding TM, the authors reported that they would not make recommendations until its effects were further studied. A recently published randomized clinical trial (the SCARLET randomized clinical trial) also failed to demonstrate a significant reduction in mortality on D28 in patients with SIC as a consequence of the use of human recombinant thrombomodulin[34]. Some authors suggested that the start of administration of recombinant TM could have been delayed in relation to the onset of inflammatory reactions and the activation of the coagulation cascade, and these authors question whether there is a profile of sepsis presentation that would benefit more from its use[49].

Sepsis is a serious clinical syndrome that requires advanced life support, and a diagnosis should be made as early as possible since mortality increases in patients with greater hemodynamic impairment, as shown by the evaluation of these patients. With the growing knowledge on sepsis, a new challenge has become evident: improving post-sepsis quality of life. Despite the severity of sepsis and the difficulties related to its diagnosis and treatment, survival has improved. However, the risk of reinfection is greater in patients who have sepsis, in addition to the greater propensity to exhibit serious injuries or enough to compromise the patients' ability to maintain self-care[50,51]. The work by Westphal *et al*[52] analyzed 217 inpatients with sepsis, with only 63 out of 112 patients experiencing high survival of more than 2 years after discharge. Among the survivors, 36 answered a quality of life questionnaire, and the following was observed from the answers: A significant reduction in functional

capacity, vitality, and mental health; The presence of pain; Worse general health status; and Main physical and emotional aspects.

ARTICLE HIGHLIGHTS

Research background

High mobility group box 1 (HMGB1) has been studied as a molecule associated with severe outcomes in sepsis and thrombomodulin (TM) seems to decrease HMGB1 proinflammatory activity.

Research motivation

We aimed to investigate the role of the thrombomodulin/high mobility group box 1 (T/H) ratio, in the first 24 h, in patients with sepsis.

Research objectives

To test the hypothesis that higher ratios would be associated with better outcomes.

Research methods

We studied twenty patients diagnosed with sepsis. They were followed until they left the intensive care unit or until they achieved 28 d of hospitalization. The following clinical outcomes were observed: Sequential Organ Failure Assessment (SOFA) score; Need for mechanical ventilation; Presence of septic shock; Occurrence of sepsis-induced coagulopathy; Need for renal replacement therapy (RRT); and Death.

Research results

The results showed that patients with SOFA scores greater than or equal to 12 points and those who need RRT had higher serum levels of TM and therefore higher T/H ratio.

Research conclusions

The authors concluded that higher serum levels of TM and, therefore, higher T/H ratio in the first 24 h after the diagnosis of sepsis were associated with a more severe disease.

Research perspectives

As this was a single center study, we cannot extrapolate the results to the general population. Further studies with bigger samples and at different centers are needed.

ACKNOWLEDGEMENTS

The authors thank the ICU staff for being so kind with all their patients.

REFERENCES

1 **Singer M**, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**: 801-810 [PMID: 26903338 DOI: 10.1001/jama.2016.0287]

2 **Sales Júnior JA**, David CM, Hatum R, Souza PC, Japiassú A, Pinheiro CT, Friedman G, Silva OB, Dias MD, Koterba E, Dias FS, Piras C, Luiz RR, Grupo de Estudo de Sepse do Fundo AMIB. [An epidemiological study of sepsis in Intensive Care Units: Sepsis Brazil study]. *Rev Bras Ter Intensiva* 2006; **18**: 9-17 [PMID: 25310321 DOI: 10.1590/S0103-507X2006000100003]

3 **Rochwerg B**, Oczkowski SJ, Siemieniuk RAC, Agoritsas T, Belley-Cote E, D'Aragon F, Duan E, English S, Gossack-Keenan K, Alghuroba M, Szczeklik W, Menon K, Alhazzani W, Sevransky J, Vandvik PO, Annane D, Guyatt G. Corticosteroids in Sepsis: An Updated Systematic Review and Meta-Analysis. *Crit Care Med* 2018; **46**: 1411-1420 [PMID: 29979221 DOI: 10.1097/CCM.0000000000003262]

4 **Lamontagne F**, Rochwerg B, Lytvyn L, Guyatt GH, Møller MH, Annane D, Kho ME, Adhikari NKJ, Machado F, Vandvik PO, Dodek P, Leboeuf R, Briel M, Hashmi M, Camsooksai J, Shankar-Hari M, Baraki MK, Fugate K, Chua S, Marti C, Cohen D, Botton E, Agoritsas T, Siemieniuk RAC. Corticosteroid therapy for sepsis: a clinical practice guideline. *BMJ* 2018; **362**: k3284 [PMID: 30097460 DOI: 10.1136/bmj.k3284]

5 **Fisher CJ Jr**, Agosti JM, Opal SM, Lowry SF, Balk RA, Sadoff JC, Abraham E, Schein RM, Benjamin E.

Treatment of septic shock with the tumor necrosis factor receptor:Fc fusion protein. The Soluble TNF Receptor Sepsis Study Group. *N Engl J Med* 1996; **334**: 1697-1702 [PMID: 8637514 DOI: 10.1056/NEJM199606273342603]

6 **Shimaoka M**, Park EJ. Advances in understanding sepsis. *Eur J Anaesthesiol Suppl* 2008; **42**: 146-153 [PMID: 18289433 DOI: 10.1017/S0265021507003389]

7 **Takehara K**, Murakami T, Kuwahara-Arai K, Iba T, Nagaoka I, Sakamoto K. Evaluation of the effect of recombinant thrombomodulin on a lipopolysaccharide-induced murine sepsis model. *Exp Ther Med* 2017; **13**: 2969-2974 [PMID: 28587368 DOI: 10.3892/etm.2017.4308]

8 **Iba T**, Miki T, Hashiguchi N, Yamada A, Nagaoka I. Combination of antithrombin and recombinant thrombomodulin attenuates leukocyte-endothelial interaction and suppresses the increase of intrinsic damage-associated molecular patterns in endotoxemic rats. *J Surg Res* 2014; **187**: 581-586 [PMID: 24296334 DOI: 10.1016/j.jss.2013.10.058]

9 **Matzinger P**. Essay 1: the Danger model in its historical context. *Scand J Immunol* 2001; **54**: 4-9 [PMID: 11439142 DOI: 10.1046/j.1365-3083.2001.00974.x]

10 **Abdulmahdi W**, Patel D, Rabadi MM, Azar T, Jules E, Lipphardt M, Hashemiyoon R, Ratliff BB. HMGB1 redox during sepsis. *Redox Biol* 2017; **13**: 600-607 [PMID: 28806702 DOI: 10.1016/j.redox.2017.08.001]

11 **Janeway C**. Immunogenicity signals 1,2,3 ... and 0. *Immunol Today* 1989; **10**: 283-286 [PMID: 2590379 DOI: 10.1016/0167-5699(89)90081-9]

12 **Tang D**, Kang R, Zeh HJ 3rd, Lotze MT. High-mobility group box 1, oxidative stress, and disease. *Antioxid Redox Signal* 2011; **14**: 1315-1335 [PMID: 20969478 DOI: 10.1089/ars.2010.3356]

13 **Ito T**, Kawahara K, Nakamura T, Yamada S, Nakamura T, Abeyama K, Hashiguchi T, Maruyama I. High-mobility group box 1 protein promotes development of microvascular thrombosis in rats. *J Thromb Haemost* 2007; **5**: 109-116 [PMID: 17239166 DOI: 10.1111/j.1538-7836.2006.02255.x]

14 **Okamoto K**, Tamura T, Sawatsubashi Y. Sepsis and disseminated intravascular coagulation. *J Intensive Care* 2016; **4**: 23 [PMID: 27011792 DOI: 10.1186/s40560-016-0149-0]

15 **Ito T**, Kawahara K, Okamoto K, Yamada S, Yasuda M, Imaizumi H, Nawa Y, Meng X, Shrestha B, Hashiguchi T, Maruyama I. Proteolytic cleavage of high mobility group box 1 protein by thrombin-thrombomodulin complexes. *Arterioscler Thromb Vasc Biol* 2008; **28**: 1825-1830 [PMID: 18599803 DOI: 10.1161/ATVBAHA.107.150631]

16 **Iba T**, Nakarai E, Takayama T, Nakajima K, Sasaoka T, Ohno Y. Combination effect of antithrombin and recombinant human soluble thrombomodulin in a lipopolysaccharide induced rat sepsis model. *Crit Care* 2009; **13**: R203 [PMID: 20003418 DOI: 10.1186/cc8210]

17 **Xie K**, Yu Y, Pei Y, Hou L, Chen S, Xiong L, Wang G. Protective effects of hydrogen gas on murine polymicrobial sepsis *via* reducing oxidative stress and HMGB1 release. *Shock* 2010; **34**: 90-97 [PMID: 19997046 DOI: 10.1097/SHK.0b013e3181cdc4ae]

18 **Aikawa N**, Shimazaki S, Yamamoto Y, Saito H, Maruyama I, Ohno R, Hirayama A, Aoki Y, Aoki N. Thrombomodulin alfa in the treatment of infectious patients complicated by disseminated intravascular coagulation: subanalysis from the phase 3 trial. *Shock* 2011; **35**: 349-354 [PMID: 21068698 DOI: 10.1097/SHK.0b013e318204c019]

19 **ARDS Definition Task Force**. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012; **307**: 2526-2533 [PMID: 22797452 DOI: 10.1001/jama.2012.5669]

20 **Rodrigues-Filho EM**, Fernandes R, Garcez A. SOFA in the first 24 hours as an outcome predictor of acute liver failure. *Rev Bras Ter Intensiva* 2018; **30**: 64-70 [PMID: 29742228 DOI: 10.5935/0103-507x.20180012]

21 **Hissa PNG**, Hissa MRN, Araújo PSR. Análise comparativa entre dois escores na previsão de mortalidade em unidade terapia intensiva. *Revista da Sociedade Brasileira de Clínica Médica* 2013; **11**: 21-26

22 **Bellomo R**, Kellum JA, Ronco C, Wald R, Martensson J, Maiden M, Bagshaw SM, Glassford NJ, Lankadeva Y, Vaara ST, Schneider A. Acute kidney injury in sepsis. *Intensive Care Med* 2017; **43**: 816-828 [PMID: 28364303 DOI: 10.1007/s00134-017-4755-7]

23 **Reference Keys**. *Kidney Int Suppl (2011)* 2012; **2**: 4 [PMID: 25018913 DOI: 10.1038/kisup.2012.4]

24 **Iba T**, Nisio MD, Levy JH, Kitamura N, Thachil J. New criteria for sepsis-induced coagulopathy (SIC) following the revised sepsis definition: a retrospective analysis of a nationwide survey. *BMJ Open* 2017; **7**: e017046 [PMID: 28963294 DOI: 10.1136/bmjopen-2017-017046]

25 **Yamakawa K**, Yoshimura J, Ito T, Hayakawa M, Hamasaki T, Fujimi S. External Validation of the Two Newly Proposed Criteria for Assessing Coagulopathy in Sepsis. *Thromb Haemost* 2019; **119**: 203-212 [PMID: 30593085 DOI: 10.1055/s-0038-1676610]

26 **Centers for Disease Control and Prevention**. Epi Info™, version 3.5.4. for windows, Division of Health Informatics & Surveillance (DHIS), Center for Surveillance, Epidemiology & Laboratory Services (CSELS). Available from: https://www.cdc.gov/epiinfo/

27 **Morello LG**, Dalla-Costa LM, Fontana RM, Netto ACSO, Petterle RR, Conte D, Pereira LA, Krieger MA, Raboni SM. Assessment of clinical and epidemiological characteristics of patients with and without sepsis in intensive care units of a tertiary hospital. *Einstein (Sao Paulo)* 2019; **17**: eAO4476 [PMID: 30994701 DOI: 10.31744/einstein_journal/2019AO4476]

28 **Laterre PF**, Levy MM, Wittebole X, Dugernier T, Francois B, Opal SM. Should we continue to test soluble thrombomodulin, or other systemic anticoagulants, as a life-saving therapy for sepsis-induced coagulopathy? *Anaesth Crit Care Pain Med* 2019; **38**: 419-421 [PMID: 31585759 DOI: 10.1016/j.accpm.2019.09.003]

29 **Rhee C**, Jones TM, Hamad Y, Pande A, Varon J, O'Brien C, Anderson DJ, Warren DK, Dantes RB, Epstein L, Klompas M; Centers for Disease Control and Prevention (CDC) Prevention Epicenters Program. Prevalence, Underlying Causes, and Preventability of Sepsis-Associated Mortality in US Acute Care Hospitals. *JAMA Netw Open* 2019; **2**: e187571 [PMID: 30768188 DOI: 10.1001/jamanetworkopen.2018.7571]

30 **Gibot S**, Massin F, Cravoisy A, Barraud D, Nace L, Levy B, Bollaert PE. High-mobility group box 1 protein plasma concentrations during septic shock. *Intensive Care Med* 2007; **33**: 1347-1353 [PMID: 17525840 DOI: 10.1007/s00134-007-0691-2]

31 **Zheng S**, Weng Q, Wu W, Ding G. Blood purification treatment initiated at the time of sepsis diagnosis effectively attenuates serum HMGB1 upregulation and improves patient prognosis. *Exp Ther Med* 2017; **14**: 3029-3035 [PMID: 28912856 DOI: 10.3892/etm.2017.4854]

32 **Malig MS**, Jenne CN, Ball CG, Roberts DJ, Xiao Z, Kirkpatrick AW. High Mobility Group Box-1 Protein and Outcomes in Critically Ill Surgical Patients Requiring Open Abdominal Management. *Mediators Inflamm* 2017; **2017**: 6305387 [PMID: 28286376 DOI: 10.1155/2017/6305387]

33 **Alpkvist H**, Athlin S, Mölling P, Norrby-Teglund A, Strålin K. High HMGB1 levels in sputum are related to pneumococcal bacteraemia but not to disease severity in community-acquired pneumonia. *Sci Rep* 2018; **8**: 13428 [PMID: 30194360 DOI: 10.1038/s41598-018-31504-4]

34 **Vincent JL**, Francois B, Zabolotskikh I, Daga MK, Lascarrou JB, Kirov MY, Pettilä V, Wittebole X, Meziani F, Mercier E, Lobo SM, Barie PS, Crowther M, Esmon CT, Fareed J, Gando S, Gorelick KJ, Levi M, Mira JP, Opal SM, Parrillo J, Russell JA, Saito H, Tsuruta K, Sakai T, Fineberg D; SCARLET Trial Group. Effect of a Recombinant Human Soluble Thrombomodulin on Mortality in Patients With Sepsis-Associated Coagulopathy: The SCARLET Randomized Clinical Trial. *JAMA* 2019; **321**: 1993-2002 [PMID: 31104069 DOI: 10.1001/jama.2019.5358]

35 **Russell JA**, Rush B, Boyd J. Pathophysiology of Septic Shock. *Crit Care Clin* 2018; **34**: 43-61 [PMID: 29149941 DOI: 10.1016/j.ccc.2017.08.005]

36 **Bone RC**, Grodzin CJ, Balk RA. Sepsis: a new hypothesis for pathogenesis of the disease process. *Chest* 1997; **112**: 235-243 [PMID: 9228382 DOI: 10.1378/chest.112.1.235]

37 **Siqueira-Batista R**, Gomes AP, Calixto-Lima L, Vitorino RR, Perez MC, Mendonça EG, Oliveira MG, Geller M. Sepsis: an update. *Rev Bras Ter Intensiva* 2011; **23**: 207-216 [PMID: 25299722 DOI: 10.1590/S0103-507X2011000200014]

38 **Wan L**, Bagshaw SM, Langenberg C, Saotome T, May C, Bellomo R. Pathophysiology of septic acute kidney injury: what do we really know? *Crit Care Med* 2008; **36** Suppl 4: S198-S203 [PMID: 18382194 DOI: 10.1097/CCM.0b013e318168ccd5]

39 **Levy MM**, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, Bion J, Schorr C, Artigas A, Ramsay G, Beale R, Parker MM, Gerlach H, Reinhart K, Silva E, Harvey M, Regan S, Angus DC; Surviving Sepsis Campaign. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med* 2010; **38**: 367-374 [PMID: 20035219 DOI: 10.1097/CCM.0b013e3181cb0cdc]

40 **Okamoto TY**, Dias JCY, Taguti P, Sacon MF, Kauss IAM, Carrilho CMD de M, Cardoso LTQ, Grion CMC, Matsuo T. Acute renal injury in patients with severe sepsis: prognostic factors. *Scientia Medica* 2012; **22**: 138-141

41 **Małyszko J**, Małyszko JS, Myśliwiec M. Endothelial cell injury markers in chronic renal failure on conservative treatment and continuous ambulatory peritoneal dialysis. *Kidney Blood Press Res* 2004; **27**: 71-77 [PMID: 14691349 DOI: 10.1159/000075810]

42 **Iba T**, Levy JH, Raj A, Warkentin TE. Advance in the Management of Sepsis-Induced Coagulopathy and Disseminated Intravascular Coagulation. *J Clin Med* 2019; **8** [PMID: 31121897 DOI: 10.3390/jcm8050728]

43 **Delabranche X**, Helms J, Meziani F. Immunohaemostasis: a new view on haemostasis during sepsis. *Ann Intensive Care* 2017; **7**: 117 [PMID: 29197958 DOI: 10.1186/s13613-017-0339-5]

44 **Timmermans K**, Kox M, Scheffer GJ, Pickkers P. DANGER IN THE INTENSIVE CARE UNIT: DAMPS IN CRITICALLY ILL PATIENTS. *Shock* 2016; **45**: 108-116 [PMID: 26513703 DOI: 10.1097/SHK.0000000000000506]

45 **Iba T**, Saitoh D. Efficacy of antithrombin in preclinical and clinical applications for sepsis-associated disseminated intravascular coagulation. *J Intensive Care* 2014; **2**: 66 [PMID: 25705422 DOI: 10.1186/s40560-014-0051-6]

46 **van der Poll T**. Recombinant Human Soluble Thrombomodulin in Patients With Sepsis-Associated Coagulopathy: Another Negative Sepsis Trial? *JAMA* 2019; **321**: 1978-1980 [PMID: 31104068 DOI: 10.1001/jama.2019.5792]

47 **Ito T**, Thachil J, Asakura H, Levy JH, Iba T. Thrombomodulin in disseminated intravascular coagulation and other critical conditions-a multi-faceted anticoagulant protein with therapeutic potential. *Crit Care* 2019; **23**: 280 [PMID: 31416465 DOI: 10.1186/s13054-019-2552-0]

48 **Rhodes A**, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med* 2017; **45**: 486-552 [PMID: 28098591 DOI: 10.1097/CCM.0000000000002255]

49 **Hasegawa D**, Nishida O. Individualized recombinant human thrombomodulin (ART-123) administration in sepsis patients based on predicted phenotypes. *Crit Care* 2019; **23**: 231 [PMID: 31234901 DOI: 10.1186/s13054-019-2521-7]

50 **Prescott HC**, Angus DC. Enhancing Recovery From Sepsis: A Review. *JAMA* 2018; **319**: 62-75 [PMID: 29297082 DOI: 10.1001/jama.2017.17687]

51 **Prescott HC**, Langa KM, Iwashyna TJ. Readmission diagnoses after hospitalization for severe sepsis and other acute medical conditions. *JAMA* 2015; **313**: 1055-1057 [PMID: 25756444 DOI: 10.1001/jama.2015.1410]

52 **Westphal GA**, Vieira KD, Orzechowski R, Kaefer KM, Zaclikevis VR, Mastroeni MF. [Analysis of quality of life following hospital discharge among survivors of severe sepsis and septic shock]. *Rev Panam Salud Publica* 2012; **31**: 499-505 [PMID: 22858817 DOI: 10.1590/s1020-49892012000600008]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 2220-3141 (online)

World Journal of

Critical Care Medicine

World J Crit Care Med 2020 December 18; 9(5): 74-98

Published by Baishideng Publishing Group Inc

World Journal of Critical Care Medicine

Contents

Continuous Publication Volume 9 Number 5 December 18, 2020

ORIGINAL ARTICLE

Retrospective Study

SYSTEMATIC REVIEWS

World Journal of Critical Care Medicine

Continuous Publication Volume 9 Number 5 December 18, 2020

Contents

ABOUT COVER

Editorial board member of *World Journal of Critical Care Medicine*, Dr. Ahmet Eroglu is a Distinguished Professor in the Department of Anesthesia and Reanimation at the Karadeniz Technical University in Trabzon, Turkey. He is a specialist and has numerous publications in anesthesiology and critical care medicine. After Dr. Eroglu graduated in Medicine from Istanbul University Cerrahpasa School of Medicine, Istanbul, in 1986, he undertook postgraduate studies in anesthesia and critical care medicine, obtaining Doctorates in 1999 and 2012, respectively, at Karadeniz Technical University. His research interests have focused on general and local anesthetics, regional anesthesia, hypotensive epidural anesthesia, orthopedic anesthesia, postoperative patient-controlled analgesia, hazards of anesthetic gases, clinical toxicology, immune nutrition, ischemia-reperfusion injury, acute respiratory distress syndrome, and critical care medicine. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of the *World Journal of Critical Care Medicine* (*WJCCM*, *World J Crit Care Med*) is to provide scholars and readers from various fields of critical care medicine with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCCM mainly publishes articles reporting research results and findings obtained in the field of critical care medicine and covering a wide range of topics including acute kidney failure, acute respiratory distress syndrome and mechanical ventilation, application of bronchofiberscopy in critically ill patients, cardiopulmonary cerebral resuscitation, coagulant dysfunction, continuous renal replacement therapy, fluid resuscitation and tissue perfusion, hemodynamic monitoring and circulatory support, ICU management and treatment control, sedation and analgesia, severe infection, *etc*.

INDEXING/ABSTRACTING

The *WJCCM* is now indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Continuous Publication

EDITORS-IN-CHIEF
KLE Hon

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

PUBLICATION DATE
December 18, 2020

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2020 December 18; 9(5): 74-87

DOI: 10.5492/wjccm.v9.i5.74

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Retrospective Study

National preparedness survey of pediatric intensive care units with simulation centers during the coronavirus pandemic

Kamal Abulebda, Rami A Ahmed, Marc A Auerbach, Anna M Bona, Lauren E Falvo, Patrick G Hughes, Isabel T Gross, Elisa J Sarmiento, Paul R Barach

ORCID number: Kamal Abulebda 0000-0002-7372-2632; Rami A Ahmed 0000-0001-8518-6083; Marc A Auerbach 0000-0002-3796-4300; Anna M Bona 0000-0001-9603-4288; Lauren E Falvo 0000-0001-5133-5247; Patrick G Hughes 0000-0002-0073-6961; Isabel T Gross 0000-0003-4410-6758; Elisa J Sarmiento 0000-0001-7283-9938; Paul R Barach 0000-0002-7906-698X.

Author contributions: Abulebda K, Ahmed RA, Auerbach MA, and Barach PR were the leaders of this project and were involved in the conception and design of the project, reviewing the available pertinent literature, data manuscript collection, drafting the initial draft of the manuscript, and final approval of the manuscript; Bona AM, Falvo LE, Hughes PG, Gross IT, and Sarmiento EJ were involved in the conception and design of the project, met regularly with the project leader to review preliminary data, analyzed the data, performed critical revisions of the manuscript, and granted final approval of the manuscript.

Institutional review board statement: In accordance with 45 CFR 46.101(b) and/or IU HRPP Policy, the above-referenced protocol is granted an exemption. Exemption of this submission is

Kamal Abulebda, Department of Pediatrics, Division of Critical Care, Indiana University School of Medicine, Riley Hospital for Children at Indiana University Health, Indianapolis, IN 46202, United States

Rami A Ahmed, Anna M Bona, Lauren E Falvo, Elisa J Sarmiento, Department of Emergency Medicine, School of Medicine, Indiana University, Indianapolis, IN 46202, United States

Marc A Auerbach, Department of Pediatrics, Division of Pediatrics Emergency Medicine, Yale University School of Medicine, New Haven, CT 06504, United States

Patrick G Hughes, Department of Integrated Medical Science, Florida Atlantic University, Boca Raton, FL 33431, United States

Isabel T Gross, Department of Emergency Medicine, Yale University School of Medicine, New Haven, CT 06504, United States

Paul R Barach, Department of Pediatrics, Wayne State University School of Medicine, Detroit, MI 48202, Jefferson College of Population Health, Philadelphia, PA, 19107, United States

Corresponding author: Kamal Abulebda, MD, Associate Professor, Doctor, Department of Pediatrics, Division of Critical Care, Indiana University School of Medicine, Riley Hospital for Children at Indiana University Health, Dr, Phase 2, Room 4900, Indianapolis, IN 46202, United States. kabulebd@iupui.edu

Abstract

BACKGROUND

The coronavirus disease pandemic caught many pediatric hospitals unprepared and has forced pediatric healthcare systems to scramble as they examine and plan for the optimal allocation of medical resources for the highest priority patients. There is limited data describing pediatric intensive care unit (PICU) preparedness and their health worker protections.

AIM

To describe the current coronavirus disease 2019 (COVID-19) preparedness efforts among a set of PICUs within a simulation-based network nationwide.

METHODS

based on your agreement to abide by the policies and procedures of The Indiana University Human Research Protection Program (HRPP).

Informed consent statement: Patients were not required to give informed consent to the study because this study was a survey-based study and did not include any human subjects or patients.

Conflict-of-interest statement: None of the authors have any conflict of interest to disclose.

Data sharing statement: All authors agree on regulations and policies of the data sharing agreements.

Manuscript source: Unsolicited manuscript

Specialty type: Critical care medicine

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D, D
Grade E (Poor): 0

Received: August 14, 2020
Peer-review started: August 14, 2020
First decision: September 21, 2020
Revised: October 4, 2020
Accepted: October 23, 2020

A cross-sectional multi-center national survey of PICU medical director(s) from children's hospitals across the United States. The questionnaire was developed and reviewed by physicians with expertise in pediatric critical care, disaster readiness, human factors, and survey development. Thirty-five children's hospitals were identified for recruitment through a long-established national research network. The questions focused on six themes: (1) PICU and medical director demographics; (2) Pediatric patient flow during the pandemic; (3) Changes to the staffing models related to the pandemic; (4) Use of personal protective equipment (PPE); (5) Changes in clinical practice and innovations; and (6) Current modalities of training including simulation.

RESULTS

We report on survey responses from 22 of 35 PICUs (63%). The majority of PICUs were located within children's hospitals (87%). All PICUs cared for pediatric patients with COVID-19 at the time of the survey. The majority of PICUs (83.4%) witnessed decreases in non-COVID-19 patients, 43% had COVID-19 dedicated units, and 74.6% pivoted to accept adult COVID-19 patients. All PICUs implemented changes to their staffing models with the most common changes being changes in COVID-19 patient room assignment in 50% of surveyed PICUs and introducing remote patient monitoring in 36% of the PICU units. Ninety-five percent of PICUs conducted training for donning and doffing of enhanced PPE. Even 6 months into the pandemic, one-third of PICUs across the United States reported shortages in PPE. The most common training formats for PPE were hands-on training (73%) and video-based content (82%). The most common concerns related to COVID-19 practice were changes in clinical protocols and guidelines (50%). The majority of PICUs implemented significant changes in their airway management (82%) and cardiac arrest management protocols in COVID-19 patients (68%). Simulation-based training was the most commonly utilized training modality (82%), whereas team training (73%) and team dynamics (77%) were the most common training objectives.

CONCLUSIONS

A substantial proportion of surveyed PICUs reported on large changes in their preparedness and training efforts before and during the pandemic. PICUs implemented broad strategies including modifications to staffing, PPE usage, workflow, and clinical practice, while using simulation as the preferred training modality. Further research is needed to advance the level of preparedness, support staff assuredness, and support deep learning about which preparedness actions were effective and what lessons are needed to improve PICU care and staff protection for the next COVID-19 patient waves.

Key Words: COVID-19; Pediatric intensive care unit; Simulation; Practice innovations; Training; Preparedness

Core Tip: The coronavirus disease 2019 pandemic has forced the United States healthcare system to examine the allocation of medical resources to the highest priority patients, including the pediatric population. In this cross-sectional multicenter national survey, we provide a description of the current preparedness efforts among a set of leading United States children's hospitals' pediatric intensive care units during the early months of the pandemic. This survey demonstrated that several key strategies have been implemented, including modifications to staffing, personal protective equipment usage, and workflows and changes in acute resuscitation and airway management, treatment protocols and procedures to limit personnel's exposure to the contagion, while using simulation as the preferred training modality.

Citation: Abulebda K, Ahmed RA, Auerbach MA, Bona AM, Falvo LE, Hughes PG, Gross IT, Sarmiento EJ, Barach PR. National preparedness survey of pediatric intensive care units with simulation centers during the coronavirus pandemic. *World J Crit Care Med* 2020; 9(5): 74-87

Article in press: October 23, 2020
Published online: December 18, 2020

P-Reviewer: Jeong KY, Lalmuanawma S, Mohammadi M, Ooi L, Wang R
S-Editor: Huang P
L-Editor: Filipodia
P-Editor: Li JH

URL: https://www.wjgnet.com/2220-3141/full/v9/i5/74.htm
DOI: https://dx.doi.org/10.5492/wjccm.v9.i5.74

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has forced healthcare systems to examine the judicious allocation of scarce medical resources to the highest priority patients, including the pediatric population[1]. Recent studies report pediatric populations have a lower incidence and typically, a less severe presentation, as compared to adults[2]. Some children, particularly with co-morbidities, are more likely to develop critical illnesses such as respiratory and cardiac failure or shock that may require invasive respiratory support or extracorporeal hemodynamic support[3]. Recently, emerging data are suggesting, however, a more serious illness in kids, with hundreds of children sickened with severe illness due to COVID-19, now named multisystem inflammatory syndrome in children[4].

Diagnostic and therapeutic guidelines used for children are commonly extrapolated from studies conducted in adults. The Society of Critical Care Medicine published a national survey of more than 4500 intensive care specialists to assess adult intensive care unit (ICU) preparedness. This survey demonstrated that adult ICU settings are preparing for COVID-19 patient care by enacting a myriad of measures including: Preparing in-hospital non-ICU space, canceling elective surgeries, and preparing temporary spaces and external facilities[5]. Reviews of adult ICU preparedness for pandemics have focused on concepts of infection control and optimal ways to increase staffing and surge capacity[6]. Pediatric preparedness for COVID-19 is distinct from adult preparedness due to important physiological and equipment differences, distinct differences in pediatric COVID-19 presentations, the child's stage of development, and the intimate need for parent involvement as part of the care delivery model.

It is important to assess pediatric ICU preparedness to identify gaps and inform improvements as we prepare for present and future waves of the COVID-19 pandemic. Most children's hospitals in response to the pandemic have rapidly escalated their health systems preparedness and implemented innovative processes to prevent disease transmission and prepare their staff to care for COVID-19 patients[7,8]. Despite a widely accepted standard of care and national accreditation for pandemics and mass disasters for neonatal and pediatric critical care in the United States, recent data suggest that the United States system lacks adequate surge capacity and would benefit from a well-organized, nationally directed and cohesive approach[9,10].

There are limited data describing the extent of the actual changes implemented by pediatric ICUs (PICUs) and their approaches to improve pandemic their preparedness[11]. This survey aims to describe the current: (1) Preparedness efforts by a group of leading United States children's hospitals' PICUs; (2) Changes in policies/procedures /guidelines; and (3) Training modalities and innovations including use of simulation for COVID-19 care.

MATERIALS AND METHODS

Survey design

We conducted a cross-sectional multi-center national survey of PICU medical director(s) across children's hospitals in the United States. An established team of researchers designed and analyzed the survey. This survey was reviewed and approved by the local institutional review board at Indiana University Health.

PICUs

Thirty-five children's hospitals were identified for recruitment through an established national research network "Improving Pediatric Acute Care Through Simulation" (ImPACTS). The ImPACTS was founded in 2013 to improve the quality of care delivered to acutely ill and injured children and has conducted multiple research projects assessing the readiness of emergency departments through mixed methods research and simulation use[12]. The survey was conducted between May 2020 and June 2020. An anonymous Qualtrics survey (www.qualtrics.com) was distributed *via* e-mail to all lead investigators of 35 leading children's hospitals across the ImPACTS network. Each network site lead was instructed to e-mail the link to their PICU

medical directors and copy the study coordinator. Three e-mail reminders were sent by the study coordinator to the medical directors 1 week apart over a 3 weeks period.

Survey development

The questionnaire was developed and reviewed by physicians and researchers with expertise in pediatric critical care, disaster readiness, and survey development. The survey was pretested for length and comprehensibility at five different PICUs not included in the survey to improve the face validity (defined as whether or not the survey measures what it is supposed to measure) and the content validity (defined as the degree to which the survey is representative of the topic). The survey was iteratively revised in three cycles based on the feedback and pilot data.

The physician survey included 49 questions in multiple parts addressing six themes: (1) PICU and medical director demographics; (2) Pediatric patient flow during the pandemic; (3) Changes to the staffing models related to the pandemic; (4) Use of personal protective equipment (PPE); (5) Changes in clinical practice and innovations; and (6) Current modalities of training including simulation. An open comment section was available at the end of the survey.

Statistical analysis

We compared the frequencies and percentages responses by testing differences using the Fisher's exact test. A statistical review of the study was performed by a biomedical statistician. All reported *P* values are based on two-sided tests.

RESULTS

A total of 35 PICUs within the network were identified. Responses from 22 PICUs (63%) were received (Table 1).

PICUs and medical director characteristics

The majority of PICUs were located within children's hospitals, either in academic (64%) or community children's hospitals (23%). The geographic distribution of these hospitals within the United States was five (23%) in the West region, eight (36%) in the Northeast region, five (23%) in the Midwest region, and four (18%) in the southeast region. All PICUs (100%) cared for pediatric patients with COVID-19 at the time of the survey. Other key PICU characteristics are summarized in Table 1.

Changes in patients flow across PICUs

The majority of PICUs (83.4%) witnessed decreases in non-COVID-19 patient care. Forty-three percent had COVID-19 dedicated units, and 74.6% pivoted to accept adult COVID-19 patients (Table 2).

Changes in the staffing model

All PICUs in the survey (100%) implemented extensive changes to their staffing model. The most common changes were patient room assignment (50%), introducing remote patient monitoring (37%), and changes in their patient triage model (32%). The majority (90%) prohibited medical students from any direct patient care, while 50% and 32%, respectively, limited but did not prohibit residents and fellows from direct patient care (Table 2).

Use of PPE

The majority of PICUs (95%) conducted training for appropriate donning and doffing of enhanced PPE. The two most common educational formats were hands-on and video-based training (73% and 82%, respectively). Dedicated staff (spotter) were reported to be used only by 50% of the respondents. The majority (63.4%) of respondents reported they had dedicated zoning to distinguish clean areas from contaminated areas to reduce the likelihood that team members would cross over between areas leading to further contamination.

All PICUs developed and implemented procedures to enhance PPE practice safely and audit the competencies of their providers. The majority of PICUs (90%) conducted procedures to enhance the safety of enhanced PPE use. One-third of PICUs reported regular shortages of PPE (Table 3).

Table 1 Hospital pediatric intensive care unit characteristics

Characteristics of the pediatric intensive care units	*n* = 22 (%)
Primary hospital setting description	
Academic children's hospital	14 (63.64)[a]
Community children's hospital	5 (22.73)
Children's hospital with a combined pediatric/adult hospital	2 (9.09)
Other	1 (4.55)
Number of children's hospitals by bed capacity	
Less than 100	4 (18.18)
100-199	4 (18.18)
200-299	5 (22.73)
300-399	5 (22.73)
400+	4 (18.18)
PICU description	
Combined PICU/Cardiac ICU	6 (27.27)
PICU with a separate CICU at our institution	11 (50.00)
PICU only/ No CICU at our institution	5 (22.73)
Number of PICU beds per institution	
< 16	6 (27.27)
16-30	10 (45.45)
31-45	4 (18.18)
> 45	2 (9.09)
Number of patients with confirmed COVID admitted to PICUs	
1-3	13 (61.90)
4-6	1 (4.76)
7-9	4 (19.05)
> 10	3 (14.29)

[a]$P < 0.05$.

COVID: Coronavirus disease; CICU: Cardiac intensive care unit; ICU: Intensive care unit; PICU: Pediatric intensive care unit.

Practice changes and innovations

The most common concerns for PICU directors related to the changing COVID-19 treatment protocols and instituting new guidelines (50%) and shortage of PPE equipment and supplies (36%). The majority implemented changes in their airway management protocols (82%). The most common innovations were decreasing the number of team members in the patient room during resuscitation and incorporating new methods of communication (73% and 86%, respectively). Other innovations included using video laryngoscopy for intubation (68%) and implementing a COVID-19 specific airway management checklist. Sixty-eight percent of PICUs implemented changes in their cardiac arrest management of COVID-19 patients. Only 36% of PICUs implemented training for managing surge capacity. The most common methods for keeping PICU providers updated and best-prepared regarding COVID-19 preparedness activities were mass e-mail messaging or virtual meetings (91% and 77%, respectively) (Table 4).

Training modalities for COVID-19

Simulation-based training was the most commonly utilized training method (82%). The most common learning objectives were enhanced team training (73%) and improved team dynamics (77%). The majority of simulation occurred in the settings of

Table 2 Preparedness efforts of pediatric intensive care units

Changes in patient flow across PICUs	*n* (%)
Changes in the average non-COVID patients seen during the COVID season	
Increase in non-COVID patients	
Decrease in non-COVID patients	19 (83.4)[a]
No change	2 (9.52)
Presence of COVID dedicated unit(s)?	
Yes	9 (42.86)
No	12 (57.14)
Change in patients age range to include adult patients?	
Yes	10 (74.62)
No	11 (52.38)
Changes in the staffing model	
Implementation of changes to the healthcare provider staffing model	
Change in length of shift	4 (18.8)
Change in providers assignment for COVID-19 patients, dedicated teams	5 (22.73)
Change in patient triaging model	7 (31.82)
Change in room assignment	11 (50.00)
Introducing remote patient monitoring in PICU	8 (36.63)
Other	5 (22.73)
Limiting the exposure of medical trainees for patients with known or suspected COVID-19	
Fellows prohibited from direct patient contact	
Fellows limited but not prohibited from direct patient care	7 (31.82)
APPs students prohibited from direct patient	10 (45.45)
APPs students limited but not prohibited from direct patient care	1 (4.55)
Residents prohibited from direct patient care	5 (22.73)
Residents limited but not prohibited from direct patient care	11 (50.00)
Medical students prohibited from direct patient care	20 (90.91)[a]
Medical students limited but not prohibited from direct patient care	1 (4.55)
No changes	

[a]$P < 0.05$.

APPs: Advanced practice providers; COVID: Coronavirus disease; PICU: Pediatric intensive care unit.

patient care areas (77%). The majority of PICU directors felt that simulation was important to prepare better their PICU staff for COVID-19 patient management while protecting their staff from contamination. Simulation experts were the most common facilitators working within the department/hospital (68%). The most common challenges to increased simulation training were related to limited financial resources (32%) and securing adequate PPE (32%) (Table 5).

DISCUSSION

COVID-19 has placed extraordinary and sustained resource demands on critical care services. This survey provides a first snapshot of the current preparedness efforts among a set of leading PICUs in the United States during the first months of the pandemic. The majority of surveyed PICUs implemented dramatic changes to their workflow and adapted their staffing models, with 43% creating dedicated COVID-19

Table 3 Personal preparedness efforts by pediatric intensive care units

The use of PPEs	*n* (%)
Current issues/limitations in regards to the utilization of PPE	
Lack of access to PPE	
Shortage in PPE	7 (31.82)
Inability to reuse PPE	1 (4.55)
No issues	14 (63.64)
Conducting training to appropriately don and doff PPE for PICU staff	
Yes	21 (95.45)[a]
No	
Unsure	
Format of PPE training	
Hands-on training	16 (72.73)[a]
Video-based content	18 (81.82)[a]
Didactic/small group training	7 (31.82)
Email material	13 (59.09)
Other	2 (9.09)
Procedures to enhance safety of PPE	
Buddy system	8 (36.36)
Increased staff	6 (27.27)
Dedicated staff, spotter	11 (50.00)
Distribution of printed safety	13 (59.09)
Other	1 (4.55)
None	2 (9.09)
Auditing PPE competencies	
Assess the performance of doffing team	14 (63.64)
Written examination	
Simulation assessment	7 (31.82)
Provide structured feedback around key competency areas	4 (18.18)
Regularly assess competencies with spot checks and/or video	6 (27.27)
None	1 (4.55)
Optimization of PPE doffing areas	
Dedicated doffing area to avoid team members from bumping into one another or equipment	4 (18.18)
Zoning to distinguish clean area from potentially contaminated areas to reduce the likelihood that team members cross over between areas spreading contamination	8 (63.64)
Use the same space for donning and doffing of PPE	14 (63.64)
Dedicated staff to observe the doffing process, Doffing spotters	7 (31.82)
Other	5 (22.73)

[a]$P < 0.05$.

PICU: Pediatric intensive care unit; PPE: Personal protective equipment.

care units. Additionally, medical trainees with different professional backgrounds were either limited or prohibited from participating in direct patient care, posing significant workload burdens on PICU staff.

In March 2020, during the peak of the pandemic in New York City, The Association of American Medical Colleges and The Liaison Committee on Medical Education issued guidance that medical students should not be involved in the care of COVID-19 patients or persons under investigation, and many medical schools near the early epicenter of the pandemic discontinued clinical rotations[13]. Surveyed directors reported that they conducted extensive training on the proper use of enhanced PPE among their providers, while a third of surveyed programs reported regular shortages in PPE. Even 6 months into the pandemic, PPE shortages continue to be reported across the United States. Beyond this, more than two-thirds of PICUs implemented innovative training for their providers targeted at modified clinical practices for airway and cardiac arrest management, while only one-third implemented surge management training. Simulation conducted *in situ* is a well-established method for effective team training and was the most common training modality in our survey and was frequently utilized to support interprofessional team training and improve team dynamics in the ICU setting[14,15].

Our survey results are the first nationwide reports from pediatric ICUs with that have active simulation programs about their state of preparedness[7,16]. PICUs initiated rapid cycle planning and implementation of changes to established childcare models to ensure that safe and effective care was being maintained. Although many adult ICUs have reported on current approaches to improve preparedness, this is the first survey outlining the detailed preparedness steps and response efforts adopted by PICUs[17].

Many PICUs encountered a dramatic decrease in the number of non-COVID-19 patients as the pandemic evolved, which has likely helped balance the need for additional resources and training for all bedside providers to care for COVID-19 patients. In this survey, one-third of PICUs reported a consistent shortage in PPEs, which is similar to what has been reported in previous pandemics and which continues to put healthcare workers at risk[18-20]. This ongoing shortage of PPE is notable given the high risk of PICU staff exposed to aerosol-generating procedures, with recent data suggesting over 3000 healthcare workers have died caring for COVID-19 patients, including several intensive care providers, and at least 500000 healthcare providers reported infected worldwide[21,22].

The findings of the survey are a reflection of the overall preparedness efforts among the participating PICUs and the changes completed in operational policies by the surveyed PICUs. These changes translate into clinical and occupational benefits and can help in optimizing the clinical services of PICUs nationwide who are under resource constraints. These benefits include protecting healthcare providers and patients from the virus exposure to reduce the infection risks, establishing a community of practice among PICU clinical services and medical directors to avoid "reinventing the wheel" during the current pandemic, and more importantly identifying how best to prepare and implement more effective operational plans for predictable future pandemics. Furthermore, this survey serves as a guide to highlight and address present PICU system vulnerabilities. It supports PICU leadership and bedside providers in providing the highest quality of care and a laser-like focus on the safety of healthcare providers.

This survey has several limitations. While 22 of 35 major leading PICU medical directors responded, this represents only a sample of all United States PICUs, which may impact the generalizability of our findings. Additionally, this survey targeted PICUs that have active simulation programs, which may reflect more well-funded facilities. The survey, nonetheless, can provide deep insights into how PICU directors and programs are adapting their training, staffing, and workflow to address the ongoing, shifting pandemic demands. Additionally, the survey responses are inherently prone to bias and may not always accurately reflect the actual practice of clinical performance but rather the policies and intent. Lastly, we did not capture certain data such as the percent decrease in non-COVID-19 patients seen or visitors' policy to the PICUs.

CONCLUSION

We conclude in this first national survey that the current preparedness efforts among PICUs in the United States during the first few months of the COVID-19 pandemic

Table 4 Preparedness efforts by pediatric intensive care units

Practice change/Innovations	*n* (%)
Concerns related to the current COVID-19 clinical practice	
Lack of clinical guidelines/protocols	5 (22.73)
Changes in guidelines/protocols	11 (50.00)
Lack of PPE training	3 (13.64)
Physician staff shortage	
RN staff shortage	2 (9.09)
Other staff shortage	1 (4.55)
Shortage in equipment/supplies	8 (36.36)
Patient surge and crowding	5 (22.73)
Other	5 (22.73)
Implementation of COVID focused airway management training	
Yes	18 (81.82)
No	3 (13.64)
Unsure	
Practice innovations for airway management	
Caring for patients with suspected or confirmed COVID in negative pressure room	14 (63.64)
Using video laryngoscopy only for intubation	15 (68.18)
Decreased clinical care team numbers at bedside	19 (86.36)[a]
Incorporating new methods of communication between team members	16 (72.73)[a]
Implementing airway management checklists	15 (68.18)
Using telemedicine/video technology	9 (40.91)
Other	2 (9.09)
Intubation of suspected or confirmed COVID patients	
By anesthesiologist who responds as part of the Airway Team	5 (22.73)
Anesthesiologist or other dedicated airway provider who is called if intubation is required	7 (31.82)
Attending physician unless the patient is suspected of having a difficult airway	12 (54.55)
Attending physician or fellow	7 (31.82)
Any appropriately trained member of the team	
Other	8 (36.36)
Implementation of COVID focused cardiac arrest management training	
Yes	15 (68.18)
No	6 (27.27)
Unsure	
Practice innovations for cardiac arrest management	
Caring for patients with suspected or confirmed COVID in negative pressure rooms only	13 (59.09)
Changing CPR practices	10 (45.45)
Decreased clinical care team numbers at bedside	16 (72.73)[a]
Incorporating new methods of communication between team members	15 (68.18)[a]
Using telemedicine/video technology	7 (31.82)
Other	4 (18.18)
Implementation of surge capacity management training	

Yes	8 (36.36)
No	13 (59.09)
Unsure	
How does your PICU keep all providers updated regarding COVID preparedness activities?	
Mass e-mails	20 (90.91)[a]
Regular in-person huddle/meetings	11 (50.00)
Virtual conferences/meetings	17 (77.27)[a]
Simulation-based	9 (40.91)
Other	

[a]$P < 0.05$.

COVID: Coronavirus disease; CPR: Cardiopulmonary resuscitation; PPE: Personal protective equipment; PICU: Pediatric intensive care unit; RN: Registered nurse.

have been highly variable, with one-third lacking adequate PPE. PICUs have implemented several strategies including modifications to staffing and workflows, changes in their acute resuscitation and airway management, treatment protocols, limiting personnel's exposure to contagion, while using simulation as the preferred training modality to support protocol changes in response to COVID-19. Our findings highlight the importance of sharing experiences among PICUs, particularly during these challenging times. Future research is needed to better appreciate the effectiveness of better PPE preparedness, workflow, and training changes. We also need to better understand what are the impacts of limiting trainees' exposure to COVID-19 care on their clinical competencies in preparation for ongoing and future pandemics.

Table 5 Preparedness efforts by pediatric intensive care units

COVID-19 training modalities	*n* (%)
Modalities currently utilized for training staff?	
Video/teleconference	17 (7.27)
Didactic	12 (54.55)
Online modules	10 (45.45)
Simulation-based training	18 (81.82)
Virtual reality	1 (4.55)
Other	
Importance of simulation-based training for the preparation of PICU staff for COVID-19 patient management	
Extremely important	9 (40.91)
Important	7 (31.82)
Neutral	1 (4.55)
Unimportant	
Not at all important	
Objectives of the simulation-based training	
PPE, donning and doffing	12 (54.55)
Individual procedural skills, *i.e.* intubation	13 (59.09)
Team training, *i.e.* CPR	16 (72.73)
Team dynamics, *i.e.* communication	17 (77.27)
Mass casualty and surge capacity management	1 (4.55)
Diagnostic testing	1 (4.55)
Facility utilization and contingency planning, use of negative pressure rooms	2 (9.09)
Tent deployment	1 (4.55)
Other	
Location of the training	
Simulation center	3 (13.64)
In situ, in its original place or location	17 (77.27)
Classroom setting	
Other format, boot camp	1 (4.55)
Simulation equipment	
High-fidelity, full body mannequin, simulator	13 (59.09)
Low-fidelity, full body mannequin, simulator	7 (31.82)
Task trainers, intubation heads, central line trainers, *etc.*	7 (31.81)
Standardized patients, actors	1 (4.55)
Virtual Reality	3 (13.64)
Other	
Participating members	
Physicians	17 (77.27)
Nurses	17 (77.27)
Respiratory therapists	15 (68.18)
Technicians	5 (22.73)
Residents/fellows	15 (68.18)

Students	
Other staff	
What simulation training was the MOST helpful	
PPE, donning and doffing	6 (27.27)
Individual procedural skills, *i.e.* intubation	8 (36.36)
Team training, *i.e.* CPR	12 (54.55)
Team dynamics, *i.e.* communication	10 (45.45)
Other	1 (4.55)
What simulation training was the LEAST helpful	
PPE, donning and doffing	3 (13.64)
Individual procedural skills, *i.e.* intubation	2 (9.09)
Team training, *i.e.* CPR	2 (9.09)
Team dynamics, *i.e.* communication	2 (9.09)
Other	8 (36.36)
Facilitators of the simulation-based training	
Presence of a simulation center	7 (31.82)
Presence of a simulation team in your department/hospital	15 (68.18)
Buy-in/support from hospital administration team	8 (36.36)
Involvement in other simulation collaborative and simulation leadership	7 (31.82)
Other	8 (36.36)
Challenges to execute simulation-based training	
Buy-in/support from hospital administration team	1 (4.55)
Financial resources	7 (31.82)
Securing adequate supplies, PPE	7 (31.82)
Staff buy-in and participation	4 (18.18)
Lack of a trained simulation team	
Lack of simulation logistics/supplies	4 (18.18)
Lack of time for preparation	5 (22.73)
Lack of desire for this form of training	1 (4.55)
Other	7 (31.82)
Development of novel or unique training equipment or training aides	
Yes, *i.e.* intubating fume hood, please share	7 (31.82)
No	10 (45.45)

COVID: Coronavirus disease; CPR: Cardiopulmonary resuscitation; PICU: Pediatric intensive care unit; PPE: Personal protective equipment.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease pandemic caught many pediatric hospitals unprepared and has forced pediatric healthcare systems to scramble as they examine and plan for the optimal allocation of medical resources for the highest priority patients.

Research motivation

To help in optimizing the clinical services of pediatric intensive care units (PICUs) nationwide under resource constraints through a reflection of the overall preparedness efforts among a set of PICUs.

Research objectives

To describe the current coronavirus disease 2019 (COVID-19) preparedness efforts among a set of PICUs within a simulation-based network nationwide.

Research methods

A cross-sectional multi-center national survey of PICU medical director(s) across children's hospitals in the United States.

Research results

Responses from 22 of 35 PICUs (63%) were received. All PICUs cared for pediatric patients with COVID-19 at the time of the survey, and the majority witnessed decreases in non-COVID-19 patients. All PICUs implemented changes to their staffing models, and 95% of PICUs conducted training for donning and doffing of enhanced personal protective equipment. The majority of PICUs implemented significant changes in their airway management (82%) and cardiac arrest management protocols in COVID-19 patients (68%). Simulation-based training was the most commonly utilized training modality (82%), whereas team training and team dynamics were the most common training objectives.

Research conclusions

The current preparedness efforts among PICUs in the United States during the first few months of the COVID-19 pandemic have been highly variable. PICUs have implemented several strategies including modifications to staffing and workflows, changes in their acute resuscitation and airway management, treatment protocols, limiting personnel's exposure to contagion, while using simulation as the preferred training modality to support protocol changes in response to COVID-19.

Research perspectives

This survey highlights the importance of sharing experiences among PICUs, particularly during these challenging times, and how to prepare and implement more effective operational plans for predictable future pandemics.

REFERENCES

1 **Emanuel EJ**, Persad G, Upshur R, Thome B, Parker M, Glickman A, Zhang C, Boyle C, Smith M, Phillips JP. Fair Allocation of Scarce Medical Resources in the Time of Covid-19. *N Engl J Med* 2020; **382**: 2049-2055 [PMID: 32202722 DOI: 10.1056/NEJMsb2005114]

2 **Sachdeva R**, Rice TB, Reisner B, Brundage N, Hulbert C, Kaminski A, Wetzel RC. The Impact of Coronavirus Disease 2019 Pandemic on U.S. and Canadian PICUs. *Pediatr Crit Care Med* 2020; **21**: e643-e650 [PMID: 32649399 DOI: 10.1097/PCC.0000000000002510]

3 **Kache S**, Chisti MJ, Gumbo F, Mupere E, Zhi X, Nallasamy K, Nakagawa S, Lee JH, Di Nardo M, de la Oliva P, Katyal C, Anand KJS, de Souza DC, Lanziotti VS, Carcillo J. COVID-19 PICU guidelines: for high- and limited-resource settings. *Pediatr Res* 2020; **88**: 705-716 [PMID: 32634818 DOI: 10.1038/s41390-020-1053-9]

4 **Feldstein LR**, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, Newburger JW, Kleinman LC, Heidemann SM, Martin AA, Singh AR, Li S, Tarquinio KM, Jaggi P, Oster ME, Zackai SP, Gillen J, Ratner AJ, Walsh RF, Fitzgerald JC, Keenaghan MA, Alharash H, Doymaz S, Clouser KN, Giuliano JS Jr, Gupta A, Parker RM, Maddux AB, Havalad V, Ramsingh S, Bukulmez H, Bradford TT, Smith LS, Tenforde MW, Carroll CL, Riggs BJ, Gertz SJ, Daube A, Lansell A, Coronado Munoz A, Hobbs CV, Marohn KL, Halasa NB, Patel MM, Randolph AG; Overcoming COVID-19 Investigators; CDC COVID-19 Response Team. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *N Engl J Med* 2020; **383**: 334-346 [PMID: 32598831 DOI: 10.1056/NEJMoa2021680]

5 **Kaplan LJ**, Kleinpell R, Maves RC, Doersam JK, Raman R, Ferraro DM. Critical Care Clinician Reports on Coronavirus Disease 2019: Results From a National Survey of 4,875 ICU Providers. *Crit Care Explor* 2020; **2**: e0125 [PMID: 32671350 DOI: 10.1097/CCE.0000000000000125]

6 **Griffin KM**, Karas MG, Ivascu NS, Lief L. Hospital Preparedness for COVID-19: A Practical Guide from a Critical Care Perspective. *Am J Respir Crit Care Med* 2020; **201**: 1337-1344 [PMID: 32298146 DOI: 10.1164/rccm.202004-1037CP]

7 **Daly Guris RJ**, Doshi A, Boyer DL, Good G, Gurnaney HG, Rosenblatt S, McGowan N, Widmeier K, Kishida M, Nadkarni V, Nishisaki A, Wolfe HA. Just-in-Time Simulation to Guide Workflow Design for Coronavirus Disease 2019 Difficult Airway Management. *Pediatr Crit Care Med* 2020; **21**: e485-e490 [PMID: 32459793 DOI: 10.1097/PCC.0000000000002435]

8 **Iqbal O'Meara AM**, Sequeira J, Miller Ferguson N. Advances and Future Directions of Diagnosis and Management of Pediatric Abusive Head Trauma: A Review of the Literature. *Front Neurol* 2020;

11: 118 [PMID: 32153494 DOI: 10.3389/fneur.2020.00118]

9 **Bohn D**, Kanter RK, Burns J, Barfield WD, Kissoon N; Task Force for Pediatric Emergency Mass Critical Care. Supplies and equipment for pediatric emergency mass critical care. *Pediatr Crit Care Med* 2011; **12**: S120-S127 [PMID: 22067920 DOI: 10.1097/PCC.0b013e318234a6b9]

10 **Barfield WD**, Krug SE, Kanter RK, Gausche-Hill M, Brantley MD, Chung S, Kissoon N; Task Force for Pediatric Emergency Mass Critical Care. Neonatal and pediatric regionalized systems in pediatric emergency mass critical care. *Pediatr Crit Care Med* 2011; **12**: S128-S134 [PMID: 22067921 DOI: 10.1097/PCC.0b013e318234a723]

11 **Morgan RW**, Kienzle M, Sen AI, Kilbaugh TJ, Dewan M, Raymond TT, Himebauch AS, Berg RA, Tegtmeyer K, Nadkarni VM, Topjian AA, Sutton RM, Wolfe HA. Pediatric Resuscitation Practices During the Coronavirus Disease 2019 Pandemic. *Pediatr Crit Care Med* 2020; **21**: e651-e660 [PMID: 32618677 DOI: 10.1097/PCC.0000000000002512]

12 Improving Pediatric Acute Care Therapy Simulation (ImPACTS). Available from: https://www.impactscollaborative.com/

13 **Whelan A**, Prescott J, Young G, Catanese VM, McKinney R. Guidance on Medical Students' Participation in Direct In-person Patient Contact Activities. Association of American Medical Colleges 2020; 6. Available from: https://www.aamc.org/system/files/2020-08/meded-August-14-Guidance-on-Medical-Students-on-Clinical-Rotations.pdf

14 **Sørensen JL**, Østergaard D, LeBlanc V, Ottesen B, Konge L, Dieckmann P, Van der Vleuten C. Design of simulation-based medical education and advantages and disadvantages of in situ simulation *versus* off-site simulation. *BMC Med Educ* 2017; **17**: 20 [PMID: 28109296 DOI: 10.1186/s12909-016-0838-3]

15 **Rosen MA**, Hunt EA, Pronovost PJ, Federowicz MA, Weaver SJ. In situ simulation in continuing education for the health care professions: a systematic review. *J Contin Educ Health Prof* 2012; **32**: 243-254 [PMID: 23280527 DOI: 10.1002/chp.21152]

16 **Jee M**, Khamoudes D, Brennan AM, O'Donnell J. COVID-19 Outbreak Response for an Emergency Department Using In Situ Simulation. *Cureus* 2020; **12**: e7876 [PMID: 32489730 DOI: 10.7759/cureus.7876]

17 **Goh KJ**, Wong J, Tien JC, Ng SY, Duu Wen S, Phua GC, Leong CK. Preparing your intensive care unit for the COVID-19 pandemic: practical considerations and strategies. *Crit Care* 2020; **24**: 215 [PMID: 32393325 DOI: 10.1186/s13054-020-02916-4]

18 **Patel A**, D'Alessandro MM, Ireland KJ, Burel WG, Wencil EB, Rasmussen SA. Personal Protective Equipment Supply Chain: Lessons Learned from Recent Public Health Emergency Responses. *Health Secur* 2017; **15**: 244-252 [PMID: 28636443 DOI: 10.1089/hs.2016.0129]

19 **Rebmann T**, Wagner W. Infection preventionists' experience during the first months of the 2009 novel H1N1 influenza A pandemic. *Am J Infect Control* 2009; **37**: e5-e16 [PMID: 20004810 DOI: 10.1016/j.ajic.2009.09.003]

20 **Srinivasan A**, Jernigan DB, Liedtke L, Strausbaugh L. Hospital preparedness for severe acute respiratory syndrome in the United States: views from a national survey of infectious diseases consultants. *Clin Infect Dis* 2004; **39**: 272-274 [PMID: 15307038 DOI: 10.1086/421777]

21 **Mantovani C**. Health workers should be top priority for vaccines - nurses' group. [Published 2020 July 27; Cited 2020 September 27]. In: yahoo news [Internet]. Available from: https://news.yahoo.com/health-workers-top-priority-vaccines-142829987.html

22 **Nguyen LH**, Drew DA, Graham MS, Joshi AD, Guo CG, Ma W, Mehta RS, Warner ET, Sikavi DR, Lo CH, Kwon S, Song M, Mucci LA, Stampfer MJ, Willett WC, Eliassen AH, Hart JE, Chavarro JE, Rich-Edwards JW, Davies R, Capdevila J, Lee KA, Lochlainn MN, Varsavsky T, Sudre CH, Cardoso MJ, Wolf J, Spector TD, Ourselin S, Steves CJ, Chan AT; COronavirus Pandemic Epidemiology Consortium. Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study. *Lancet Public Health* 2020; **5**: e475-e483 [PMID: 32745512 DOI: 10.1016/S2468-2667(20)30164-X]

World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2020 December 18; 9(5): 88-98

DOI: 10.5492/wjccm.v9.i5.88

ISSN 2220-3141 (online)

SYSTEMATIC REVIEWS

Vasopressin in vasoplegic shock: A systematic review

Andrew J Webb, Mohamed O Seisa, Tarek Nayfeh, Patrick M Wieruszewski, Scott D Nei, Nathan J Smischney

ORCID number: Andrew J Webb 0000-0003-3425-7181; Mohamed O Seisa 0000-0002-5179-4264; Tarek Nayfeh 0000-0001-9052-5537; Patrick M Wieruszewski 0000-0002-5871-5186; Scott D Nei 0000-0002-9904-5932; Nathan J Smischney 0000-0003-1051-098X.

Author contributions: All authors equally contributed to data collection, interpretation, and manuscript writing.

Conflict-of-interest statement: The authors have nothing to disclose.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Andrew J Webb, Department of Pharmacy, Oregon Health and Science University, Portland, OR 97239, United States

Mohamed O Seisa, Tarek Nayfeh, Robert D and Patricia E Kern Center For The Science of Health Care Delivery, Mayo Clinic, Rochester, MN 55905, United States

Patrick M Wieruszewski, Scott D Nei, Department of Pharmacy, Mayo Clinic, Rochester, MN 55905, United States

Nathan J Smischney, Department of Anesthesia, Mayo Clinic, Rochester, MN 55905, United States

Corresponding author: Nathan J Smischney, MD, MSc, Assistant Professor, Department of Anesthesia, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States. smischney.nathan@mayo.edu

Abstract

BACKGROUND

Vasoplegic shock is a challenging complication of cardiac surgery and is often resistant to conventional therapies for shock. Norepinephrine and epinephrine are standards of care for vasoplegic shock, but vasopressin has increasingly been used as a primary pressor in vasoplegic shock because of its unique pharmacology and lack of inotropic activity. It remains unclear whether vasopressin has distinct benefits over standard of care for patients with vasoplegic shock.

AIM

To summarize the available literature evaluating vasopressin *vs* non-vasopressin alternatives on the clinical and patient-centered outcomes of vasoplegic shock in adult intensive care unit (ICU) patients.

METHODS

This was a systematic review of vasopressin in adults (≥ 18 years) with vasoplegic shock after cardiac surgery. Randomized controlled trials, prospective cohorts, and retrospective cohorts comparing vasopressin to norepinephrine, epinephrine, methylene blue, hydroxocobalamin, or other pressors were included. The primary outcomes of interest were 30-d mortality, atrial/ventricular arrhythmias, stroke, ICU length of stay, duration of vasopressor therapy, incidence of acute kidney injury stage II-III, and mechanical ventilation for greater than 48 h.

RESULTS

A total of 1161 studies were screened for inclusion with 3 meeting inclusion criteria with a total of 708 patients. Two studies were randomized controlled trials

Manuscript source: Invited manuscript

Specialty type: Critical care medicine

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: August 1, 2020
Peer-review started: August 1, 2020
First decision: September 17, 2020
Revised: October 10, 2020
Accepted: October 26, 2020
Article in press: October 26, 2020
Published online: December 18, 2020

P-Reviewer: Eroglu A, Zhu YF
S-Editor: Gao CC
L-Editor: A
P-Editor: Li JH

and one was a retrospective cohort study. Primary outcomes of 30-d mortality, stroke, ventricular arrhythmias, and duration of mechanical ventilation were similar between groups. Conflicting results were observed for acute kidney injury stage II-III, atrial arrhythmias, duration of vasopressors, and ICU length of stay with higher certainty of evidence in favor of vasopressin serving a protective role for these outcomes.

CONCLUSION

Vasopressin was not found to be superior to alternative pressor therapy for any of the included outcomes. Results are limited by mixed methodologies, small overall sample size, and heterogenous populations.

Key Words: Vasopressins; Shock; Vasoactive agents; Treatment outcome; Vasoplegia; Arginine vasopressin

Core Tip: In this systematic review of vasopressin *vs* alternative vasoactive agents for the treatment of vasoplegic shock, vasopressin was not found to be superior to alternative pressor therapy for any of the included outcomes. However, results are limited by mixed methodologies, small overall sample size, and heterogenous populations.

Citation: Webb AJ, Seisa MO, Nayfeh T, Wieruszewski PM, Nei SD, Smischney NJ. Vasopressin in vasoplegic shock: A systematic review. *World J Crit Care Med* 2020; 9(5): 88-98
URL: https://www.wjgnet.com/2220-3141/full/v9/i5/88.htm
DOI: https://dx.doi.org/10.5492/wjccm.v9.i5.88

INTRODUCTION

Vasoplegic shock, one of the most significant complications that can arise after cardiac surgery, can be devastating and challenging to manage[1]. Vasoplegic shock is defined by low systemic vascular resistance despite adequate fluid resuscitation and a normal or increased cardiac index[2]. Post-operative vasoplegia is most common after cardiac surgery involving cardiopulmonary bypass, occurring in about 5% to 25% of patients[3]. While vasoplegic shock can occur after non-cardiac surgery[4], the most common risk factors for vasoplegia include cardiopulmonary bypass and the use of angiotensin converting enzyme inhibitors and beta blockers prior to surgery[1,5].

Vasoplegic shock involves both hyperactivity of vasodilatory pathways and resistance to and deficiency of common vasoconstrictor pathways[6,7]. Patients have been observed to mount a profound inflammatory response to cardiopulmonary bypass, leading to increased expression of nitric oxide synthase, decreased levels of vasopressin, and altered activity of catecholamine-sensitive secondary messenger systems[8,9]. Catecholamines, especially norepinephrine, have long been considered first line, but evidence supporting one therapy over another is limited and each carry the risk of adverse effects[10,11]. Other therapeutic agents targeting different pathophysiologic complications of vasoplegia include methylene blue, hydroxocobalamin, vasopressin, and angiotensin II and each carries distinct potential benefits and risks.

Vasopressin's unique pharmacology may lend it to being particularly beneficial in vasoplegic shock[12-15]. Activation of G_q-coupled vasopressin-1 (V1) receptors leads to smooth muscle contraction through the recruitment of intracellular calcium stores in the sarcoplasmic reticulum and extracellular calcium stores by opening L-type calcium channels[16,17]. There is also minimal V1 receptor expression in the pulmonary vasculature which may be of particular benefit to patients with right heart dysfunction or pulmonary hypertension[18]. Questions still remain, however, about its benefits over standard of care in shock. There is a lack of large, multi-center prospective trials addressing these questions. Thus, the aim of this systematic review was to summarize

the available literature evaluating vasopressin *vs* non-vasopressin alternatives on the clinical and patient-centered outcomes of vasoplegic shock in adult intensive care unit (ICU) patients.

MATERIALS AND METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2015 guidelines. A formal protocol does not exist for this systematic review.

Eligibility criteria

We included randomized controlled trials, prospective cohort studies, and retrospective cohort studies published in English in peer-reviewed journals. Studies were included if they studied adult patients (≥ 18 years), compared vasopressin to norepinephrine, epinephrine, hydroxocobalamin, or methylene blue, evaluated patients treated in the intensive care unit, and were suffering from post-operative vasoplegic shock. Follow-up needed to be until at least 30 d post-discharge. Studies needed to report 30-d mortality, acute kidney injury stage II-III based on Acute Kidney Injury Network classification (reference)[19], safety, ICU length of stay, mechanical ventilation duration, and duration of vasopressor therapy We excluded studies in pediatric patients, case reports, case series, review articles, letters, and notes. No restrictions were placed on the location of publication.

Data sources

A comprehensive search of several databases from each database's inception to December 6, 2019 of any language was conducted. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process and Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the reviewers. Controlled vocabulary supplemented with keywords was used to search for studies of vasoplegia/vasoplegic shock in critically ill patients. Actual strategy listing all search terms used and how they were combined is available in Supplementary 1.

Trial selection

Article titles and abstracts were screened by two independent authors (MOS and TN) for inclusion based on the aforementioned inclusion and exclusion criteria. The full text of articles included by title and abstract were then reviewed and disagreements were resolved through consensus.

Outcomes

The primary outcomes of interest were 30-d mortality, atrial/ventricular arrhythmias, vasopressor duration, stroke, ICU length of stay, proportion of patients suffering acute kidney injury, defined as acute kidney injury network stage 2 (serum creatinine [SCr] increase of 200% or urine output less than 0.5 mL/kg per hour in a 12 h period) or 3 (SCr increase of 300% or SCr greater than or equal to 4 mg/dL with an acute rise of at least 0.5 mg/dL or a urine output of less than 0.3 mL/kg/h in a 24 h period or anuria for 12 h)[19], and proportion of patients mechanically ventilated for greater than 48 h.

Methodological quality and certainty of evidence

The Cochrane Collaboration tool for assessing risk of bias was utilized to assess the quality and bias risk of included randomized controlled studies[20]. The tool assesses studies based on randomization, protocol deviation, missing outcome data, outcome measurements, and result reporting. The Newcastle Ottawa scale was used for assessing the risk of bias in observational studies[21]. The tool assesses studies based on selection methods, comparability, and outcome measurements. Discrepancies in scoring were resolved through consensus.

Data extraction

Two independent authors (MOS and TN) reviewed and extracted relevant data from included manuscripts in a standard data collection form. Collected data included publication information, protocol details, outcome measures, baseline characteristics,

and results.

Data analysis

For continuous outcomes, we gathered means and variance data [*e.g.*, standard deviation, standard error, confidence interval (CI)] and the weighted mean difference (MD). For binary outcomes, we gathered incidence data and frequencies and calculated the relative risk (RR). All statistical analyses were performed using R Core Team version 4.0.0 (2020).

RESULTS

Trial inclusion

The initial search identified 1161 studies. Following removal of duplicates and excluded records, 115 full-text articles were assessed for eligibility. Three (2.6%) of these met the inclusion criteria and were included in the analysis[23-25]. The results of the systematic search are summarized in Figure 1.

Trial characteristics

Of the 3 included studies, 2 were randomized controlled trials[24,25] and 1 was a retrospective cohort study[23]. A total of 1496 participants were included across the 3 studies (Table 1). The included studies were performed in Egypt, China, and Brazil, and publication dates spanned from 2016 to 2018. Characteristics of all of the included studies are detailed in Table 1.

Risk of bias

Overall, the risk of bias of the 2 included trials was moderate due to having some concerns in the randomization process of the 2 clinical trials[24,25]. The risk of bias for the cohort study was low[23]. The risk of summary bias is provided in Tables 2 and 3.

Outcomes

The results of included studies and the certainty of evidence are presented in Table 4 and Supplementary 2.

Thirty days mortality: Two studies were identified which reported 30-d mortality (n = 668)[23,24]. The risk of 30-d mortality was not found to differ between vasopressin as compared with norepinephrine.

Atrial/ventricular arrhythmias and stroke: Only two of the included studies reported safety events (n = 668)[23,24]. Although arrhythmias including atrial fibrillation and ventricular tachycardia occurred at a significantly higher frequency with vasopressin than norepinephrine as reported by Cheng *et al*[23] the certainty of evidence was low due to study design and imprecision. Hajjar *et al*[24] reported a similar frequency of ventricular tachycardia between the two pressors and vasopressin demonstrated a favorable profile at reducing atrial fibrillation when compared to norepinephrine. The certainty of evidence in these results was moderate. Although, neither study reported maximum dosage of study drug infusion rate, or dosage of vasopressors at the time of arrhythmia. Both studies did not report any differences in stroke.

Duration of vasopressors: Two studies reported duration of vasopressors (n = 668)[23,24]. The studies report discordant effect with one favoring use of vasopressin (MD -23, 95%CI -36.12, -9.88; moderate certainty of evidence, Hajjar *et al*[24]), while the other favoring use of norepinephrine (MD 24, 95%CI 16.32, 31.68; very low certainty of evidence, Cheng *et al*[23]).

ICU length of stay: All three studies reported ICU length of stay, although one study utilized methylene blue as the comparator (n = 40)[25], whereas the other two utilized norepinephrine (n = 668)[23,24]. No differences between vasopressin and methylene blue were found. When vasopressin was compared to norepinephrine, the two studies reported contradictory results with a longer length of stay in Cheng *et al*[23] (low certainty of evidence) and a shorter length of stay in Hajjar *et al*[24] (moderate certainty of evidence).

Acute kidney injury: Two studies reported incidence of acute kidney injury stage 2 or 3 (n = 668)[23,24]. Cheng *et al*[23] reported that vasopressin did not significantly affect the risk of acute kidney injury (very low certainty of evidence) while Hajjar *et al*[24]

Table 1 Trial characteristics

Ref.	Inclusion criteria	Exclusion criteria	Interventions (number of patients)	Age (yr)	Main outcomes
El Adawy *et al*[25], 2015	Severe sepsis diagnosed within 72 h and septic shock diagnosed within 24 h from the time of giving norepinephrine dose of greater than or equal to 0.2 μg/kg per minute, which is required to maintain the mean arterial pressure between 70 and 90 mmHg	(1) Pregnant females; (2) Patients sensitive to Methylene blue or vasopressin; (3) Patients with known G6PD deficiency; (4) Age less than 18 yr; (5) Vasospastic diathesis (*e.g.*, Raynaud's syndrome); (6) Coronary artery disease; and (7) Patients receiving mono amine oxidase inhibitors	Methylene blue (20); vasopressin (20)	55.3 ± 20.9; 59.4 ± 14.5	ICU length of stay; mean arterial pressure; central venous pressure; pulmonary artery pressure
Cheng *et al*[23], 2018	Patients with age more than 18 yr, who had left ventricular ejection fraction ≤ 35%, left ventricular end-diastolic diameter ≥ 60 mm, and New York Heart Association ≥ III), and developing postoperative vasoplegic shock (mean arterial pressure < 65 mmHg resistant to fluid challenge and cardiac index > 2.20 L/min per meter squared)	(1) Patients with chronic obstructive pulmonary disease; and (2) Adult congenital heart disease	Norepinephrine (938); vasopressin (218)	59.43 ± 11.07; 59.25 ± 12.73	30-d mortality; mechanical ventilation more than 48 h; cardiac reoperation; postoperative extracorporeal membrane oxygenation; stroke; acute kidney injury stage II/III; infection; septic shock; atrial fibrillation; ventricular arrhythmias
Hajjar *et al*[24], 2017	All adult (more than 18 yr of age) patients who were scheduled for coronary artery bypass graft surgery, valve replacement, or repair surgery with cardiopulmonary bypass who required vasopressor drugs for vasodilatory shock within 48 h after coronary artery bypass surgery weaning	(1) Aortic surgery; (2) Heart transplantation; (3) Preoperative use of vasopressor therapy; (4) Presence of a ventricular assist device other than an intra-aortic balloon pump; (5) Severe hyponatremia (< 130 mEq/L); (6) Acute coronary syndrome; (7) Acute mesenteric ischemia; (8) History of Raynaud disease; (9) Pregnancy; and (10) Neoplasm	Norepinephrine (151); vasopressin (149)	55 ± 13; 54 ± 14	Days alive and free of organ dysfunction at 28 d; stroke; acute renal failure; 30 d incidence of infection, septic shock, arrhythmias (atrial fibrillation and ventricular arrhythmias); duration of mechanical ventilation; changes in hemodynamic variables; the use of dobutamine or other vasoactive agents); incidence of digital ischemia; acute mesenteric ischemia; acute myocardial; infarction; ICU and hospital lengths of stay

G6PD: Glucose-6-phosphate dehydrogenase; ICU: Intensive care unit; mEq/L: Milliequivalents per liter.

Table 2 Risk of summary bias (randomized controlled trials)

Ref.	Overall ROB	ROB from randomization process	ROB due to deviations from intended interventions	ROB due to missing outcome data	ROB in measurement of outcomes	ROB in selection of the reported results	Other (funding, conflict of interest)
El Adawy *et al*[25], 2016	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk
Hajjar *et al*[24], 2017	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk

ROB: Risk of bias.

demonstrated a considerable reduction in the risk of acute kidney injury when compared to norepinephrine (moderate certainty of evidence). Not enough data in the studies were available to assess need for or eventual dialysis dependency.

Mechanical ventilation > 48 h: Two studies reported outcome data on mechanical ventilation > 48 h (n = 668)[23,24]. Although not significant, vasopressin was associated with less episodes of mechanical ventilation lasting more than 48 h.

DISCUSSION

In this systematic review of the literature evaluating the role of vasopressin in the

Table 3 Risk of summary bias (cohort study)

Ref.	Overall ROB	Selection	Ascertainment of exposure	Comparability	Ascertainment of outcome	Adequacy of follow up
Cheng *et al*[23], 2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

ROB: Risk of bias.

Table 4 Trial outcomes

Comparison	Vasopressin *vs* norepinephrine		Vasopressin *vs* methylene blue
Study	Hajjar *et al*[24], 2017	Cheng *et al*[23], 2018	El Adawy *et al*[25], 2016
Study design	Randomized trial	Cohort	Randomized trial
Sample size	330	338	40
30-d mortality	RR 0.97, 95%CI 0.57, 1.64; moderate	RR 3.33, 95%CI 0.93, 11.90; very low	-
Ventricular arrhythmia	RR 0.86, 95%CI 0.54, 1.35; moderate	RR 1.75, 95%CI 1.11, 2.76; very low	-
Duration of vasopressors	MD -23.00 d, 95%CI -36.12, -9.88; moderate	MD 24 d, 95%CI 16.32, 31.68; very low	-
Intensive care unit length of stay	MD -1.00 d, 95%CI -1.69, -0.31; moderate	MD 1.00 d, 95%CI 0.53, 1.47; low	MD 1.60 d, 95%CI -0.29, 3.49; very low
Stroke	RR 1.01, 95%CI 0.26, 3.98; low	RR 0.50, 95%CI 0.13, 1.97; very low	-
Acute kidney injury stage II/III	RR 0.32, 95%CI 0.21, 0.49; moderate	RR 1.12, 95%CI 0.89, 1.42; very low	-
Atrial arrhythmia	RR 0.78, 95%CI 0.67, 0.89; moderate	RR 1.70, 95%CI 1.02, 2.83; low	-
Mechanical ventilation > 48 h	RR 0.62, 95%CI 0.27, 1.46; low	RR 0.95, 95%CI 0.63, 1.42; very low	-

Data is presented as effect size, 95% confidence interval (CI), certainty of evidence. CI: Confidence interval; MD: Mean difference; RR: Relative risk.

treatment of post-operative vasoplegic shock, studies evaluating the effects on 30-d mortality, acute kidney injury stage 2-3, ICU length of stay, atrial fibrillation, ventricular arrhythmias, mechanical ventilation duration, and stroke were summarized. Meta-analysis was not feasible due to differences in methodology, patients, and procedures that led to variation in the reported results between studies.

Interest in vasopressin as treatment for vasoplegic shock has existed for a number of years due to its unique pharmacology independent of the autonomic nervous system. Current available literature, however, has been limited by small sample sizes, inconsistent populations, and varied outcomes, which has limited its use to adjunctive therapy. Insights from investigation into vasopressin's role in the treatment of septic shock, however, may supplement knowledge on vasopressin's role in vasoplegic shock. Randomized controlled trials of vasopressin in septic shock have not revealed a significant mortality benefit, but signals of preserved renal function, decreased overall pressor requirements, and largely equitable safety outcomes has changed it from salvage therapy to standard care for many patients with septic shock[26-30].

The evolution of vasopressin in septic shock may foreshadow the role of vasopressin in vasoplegic shock. Norepinephrine and epinephrine have functioned as the workhorses of vasoplegic shock management for decades and clinical experience outweighs the influence of the available literature to support the role of vasopressin. As clinical experience with vasopressin grows alongside the expansion of the literature, vasopressin utilization in vasoplegic shock without cardiogenic shock will likely increase. The results of this systematic review did not reveal any major advantages to vasopressin use but highlight the need for robust investigation into many of these outcomes.

Like other studies investigating specific pressors, 30-d mortality was not found to be different between patients who received vasopressin or norepinephrine in our systematic review. This is concordant with studies evaluating pressors in other shock states as well as studies evaluating vasopressin in septic shock. Few large randomized controlled trials have succeeded in demonstrating a reduction in mortality of a

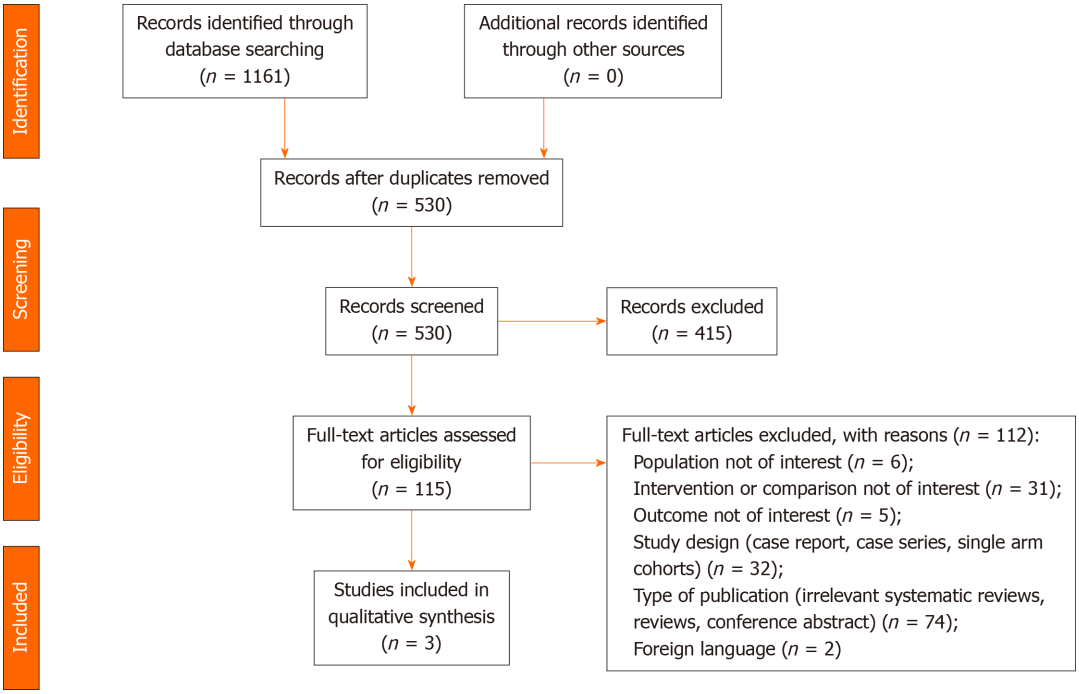

Figure 1 Study flow diagram.

singular critical care intervention, and the benefit of each individual intervention, such as the choice of vasopressor, may be better judged by its incremental benefits on morbidity and patient-specific outcomes[31-33].

No difference was revealed in ICU length of stay for vasopressin compared to norepinephrine or methylene blue in our systematic review. Of note, opposing results were reported in Hajjar *et al*[24] and Cheng *et al*[23] This imbalance may in part be due to the different baseline populations in each study, with Hajjar *et al*[24] excluding patients with left ventricular dysfunction and Cheng *et al*[23] specifically including these patients, as well as the study design (randomized clinical trial *vs* cohort study). In a meta-analysis of vasopressin in septic shock, vasopressin has not been reported to have a significant impact on ICU length of stay (mean different -0.08 d, 95%CI -0.68, 0.52)[34].

Vasopressin was not found to impact rates of stroke in patients with vasoplegic shock. Perioperative stroke after cardiac surgery is uncommon, estimated to occur in about 2% of all patients after surgery, but rates of mortality after perioperative stroke are much higher than the overall population[35,36]. While our findings indicate choice of pressor did not influence this risk, the overall sample size may be too low to estimate the impact on a rate outcome (combined event rate was 17). Potential confounders for risk of stroke, such as previous stroke, were not reported.

Given its lack of autonomic activity, one potential benefit of vasopressin is its presumed lack of arrhythmogenic properties. In our analysis, we found conflicting results from the two studies which reported ventricular and atrial arrhythmias as an outcome. This finding contrasts that of a patient-level meta-analysis of adverse event data in septic shock, which found vasopressin was associated with an absolute risk reduction of 2.8% (95%CI -0.2, -5.3) in rates of arrhythmia compared to norepinephrine[26]. Vasopressin with a catecholamine was also found to confer a lower risk of atrial arrhythmia compared to catecholamines alone in a meta-analysis of multiple shock states (RR 0.77, 95%CI 0.67, 0.88)[37]. The different results of each study in our systematic review are potentially driven by the unreported doses of pressors in Cheng *et al*[23] at the time of ventricular arrhythmia onset and the higher vasopressor needs overall in the six hours after cardiac surgery in the vasopressin group, which would be an unaccounted confounder. Of note, one should be aware that the randomized clinical trial, Hajjar *et al*[24], demonstrated reduced arrhythmogenic potential for both atrial and ventricular arrhythmias with vasopressin compared to norepinephrine unlike the cohort study of Cheng *et al*[23].

The two studies reporting vasopressor duration also had opposite effects. This discrepancy is likely due to differences in methodology and patient populations between the two studies. Considering the heterogeneity between these two studies

(see Supplementary 2) and the overall higher level of evidence in Hajjar *et al*[24], the beneficial effect on vasopressor duration in Hajjar *et al*[24] is likely a better representation of the true effect of vasopressin on this outcome, as we demonstrate for the arrhythmia and renal endpoints. Duration of vasopressor therapy may be better reported as days alive and free of vasopressors, a more patient-centered outcome[38].

Rates of stage II or III acute kidney injury were not found to be different depending on which pressor was used for vasoplegic shock. Vasopressin has unique activity at the glomerulus, including an ability to selectively constrict the efferent arteriole and not the afferent arteriole, leading to an observed increase in urine output in patients with septic shock[14,39]. In a meta-analysis of multiple shock states, vasopressin was revealed to be protective for acute kidney injury compared to alternative therapy (OR 0.52, 95%CI 0.32, 0.86). This analysis, however, is limited by mixing definitions of acute kidney injury, study designs, and indications. Need for renal replacement therapy was also not protocolized and up to the decision of the treating provider, making it difficult to compare rates between studies.

Choice of vasopressor did not impact rates of prolonged (greater than 48 h) mechanical ventilation. These results mirror other meta-analyses of patients with septic shock, where duration of mechanical ventilation (MD -0.58 h, 95%CI -1.47, 0.31) or number of ventilator-free days (13 *vs* 13) was not different between vasopressin and other pressors[26,34].

This systematic review has several limitations which should be highlighted. A large portion of our literature search met exclusion criteria because of study design or intervention which limits the sample size available for analysis. Of the studies included, only two reported many of the outcomes of interest, further limiting sample size. The studies also differ in methodology and risk of bias, making comparison of results between studies more challenging. There was also significant variation in dosing strategies of vasopressin and the reporting of concurrent vasopressor therapy which likely impacted results. This, combined with the heterogeneity revealed between the studies, reduce the reliability of the reported results.

CONCLUSION

Patients who experience vasoplegic shock suffer from significant morbidity and mortality and identification of optimal treatment modalities is of paramount importance to clinicians caring for these patients. Given its unique pharmacology, vasopressin may play a role as optimal therapy in certain patients with vasoplegic shock but should be considered as adjunct in all patients refractory to catecholamines. While current literature is promising, several questions still remain about vasopressin, such as ideal dosing strategies, timing of initiation, and in which patient populations vasopressin as a primary pressor may be ideal. Additional prospective multi-center research is warranted to investigate vasopressin's role in improving patient-centered outcomes of post-operative vasoplegic shock on a large scale.

ARTICLE HIGHLIGHTS

Research background

Vasoplegic shock is a devastating complication post-surgery, in particular cardiac surgery, that leads to poor patient outcomes. Currently, treatment for this condition consists of norepinephrine and epinephrine. However, because of vasopressin's unique pharmacology, it may have a role in the treatment of this condition.

Research motivation

Effective therapies aimed at hemodynamic preservation have not been identified in vasoplegic shock. Although norepinephrine and epinephrine are routine management, they have not proven all that effective for this condition given their hemodynamic profile and association with other complications. Vasopressin with its unique pharmacology and beneficial association with certain patient centered outcomes may be a reasonable first line alternative.

Research objectives

The aim of this systematic review was to summarize the available literature evaluating vasopressin *vs* non-vasopressin alternatives on patient-centered outcomes of

vasoplegic shock in adult intensive care unit (ICU) patients. The aim of the present study will provide useful information on whether vasopressin maybe beneficial in the treatment of vasoplegic shock.

Research methods

Randomized controlled trials, prospective cohorts, and retrospective cohorts comparing vasopressin to norepinephrine, epinephrine, methylene blue, hydroxocobalamin, or other pressors were included. The primary outcomes of interest were 30-d mortality, atrial/ventricular arrhythmias, stroke, ICU length of stay, duration of vasopressor therapy, incidence of acute kidney injury stage II-III, and mechanical ventilation for greater than 48 h. Given the mixed methodologies and heterogenous populations of the included studies and the overall small sample size, a meta-analysis was not conducted. We present weighted mean difference for continuous outcomes and relative risk for binary outcomes with associated confidence intervals.

Research results

A total of 1161 studies were screened for inclusion with 3 meeting inclusion criteria with a total of 708 patients. Two studies were randomized controlled trials and one was a retrospective cohort study. Primary outcomes of 30-d mortality, stroke, ventricular arrhythmias, and duration of mechanical ventilation were similar between groups. Conflicting results were observed for acute kidney injury stage II-III, atrial arrhythmias, duration of vasopressors, and ICU length of stay with higher certainty of evidence in favor of vasopressin serving a protective role for these outcomes. Although our results do not provide conclusive evidence of a beneficial role for vasopressin in the treatment of vasoplegic shock, we do provide some rationale as to why vasopressin could have a protective effect with regards to certain patient centered outcomes such as acute kidney injury, atrial arrhythmias, *etc*. We also provide some direction for future research in this area.

Research conclusions

Vasopressin was not found to be superior to alternative pressor therapy for any of the included outcomes. Results are limited by mixed methodologies, small overall sample size, and heterogenous populations. We identify limitations in the present systematic review such as mixed methodologies and heterogeneous populations that preclude a definitive answer on the role of vasopressin in vasoplegic shock. Future studies should have more homogenous populations with similar methodologies so that a pooled analysis can be performed to definitively answer this question.

Research perspectives

While current literature is promising, several questions still remain about vasopressin, such as ideal dosing strategies, timing of initiation, and in which patient populations vasopressin as a primary pressor may be ideal. Additional prospective multi-center research is warranted to investigate vasopressin's role in improving patient-centered outcomes of post-operative vasoplegic shock on a large scale taking into consideration dosing strategies and timing of initiation of vasoactive agents.

REFERENCES

1 **Mekontso-Dessap A**, Houël R, Soustelle C, Kirsch M, Thébert D, Loisance DY. Risk factors for post-cardiopulmonary bypass vasoplegia in patients with preserved left ventricular function. *Ann Thorac Surg* 2001; **71**: 1428-1432 [PMID: 11383777 DOI: 10.1016/s0003-4975(01)02486-9]

2 **Lambden S**, Creagh-Brown BC, Hunt J, Summers C, Forni LG. Definitions and pathophysiology of vasoplegic shock. *Crit Care* 2018; **22**: 174 [PMID: 29980217 DOI: 10.1186/s13054-018-2102-1]

3 **Levin MA**, Lin HM, Castillo JG, Adams DH, Reich DL, Fischer GW. Early on-cardiopulmonary bypass hypotension and other factors associated with vasoplegic syndrome. *Circulation* 2009; **120**: 1664-1671 [PMID: 19822810 DOI: 10.1161/CIRCULATIONAHA.108.814533]

4 **Kohl BA**, Deutschman CS. The inflammatory response to surgery and trauma. *Curr Opin Crit Care* 2006; **12**: 325-332 [PMID: 16810043 DOI: 10.1097/01.ccx.0000235210.85073.fc]

5 **Sun X**, Zhang L, Hill PC, Lowery R, Lee AT, Molyneaux RE, Corso PJ, Boyce SW. Is incidence of postoperative vasoplegic syndrome different between off-pump and on-pump coronary artery bypass grafting surgery? *Eur J Cardiothorac Surg* 2008; **34**: 820-825 [PMID: 18715792 DOI: 10.1016/j.ejcts.2008.07.012]

6 **Fischer GW**, Levin MA. Vasoplegia during cardiac surgery: current concepts and management.

Semin Thorac Cardiovasc Surg 2010; **22**: 140-144 [PMID: 21092891 DOI: 10.1053/j.semtcvs.2010.09.007]

7 **Jochberger S**, Velik-Salchner C, Mayr VD, Luckner G, Wenzel V, Falkensammer G, Ulmer H, Morgenthaler N, Hasibeder W, Dünser MW. The vasopressin and copeptin response in patients with vasodilatory shock after cardiac surgery: a prospective, controlled study. *Intensive Care Med* 2009; **35**: 489-497 [PMID: 18825368 DOI: 10.1007/s00134-008-1279-1]

8 **Downing SW**, Edmunds LH Jr. Release of vasoactive substances during cardiopulmonary bypass. *Ann Thorac Surg* 1992; **54**: 1236-1243 [PMID: 1340777 DOI: 10.1016/0003-4975(92)90113-i]

9 **Levy JH**, Tanaka KA. Inflammatory response to cardiopulmonary bypass. *Ann Thorac Surg* 2003; **75**: S715-S720 [PMID: 12607717 DOI: 10.1016/s0003-4975(02)04701-x]

10 **Stephens RS**, Whitman GJ. Postoperative Critical Care of the Adult Cardiac Surgical Patient. Part I: Routine Postoperative Care. *Crit Care Med* 2015; **43**: 1477-1497 [PMID: 25962078 DOI: 10.1097/CCM.0000000000001059]

11 **Schmittinger CA**, Torgersen C, Luckner G, Schröder DC, Lorenz I, Dünser MW. Adverse cardiac events during catecholamine vasopressor therapy: a prospective observational study. *Intensive Care Med* 2012; **38**: 950-958 [PMID: 22527060 DOI: 10.1007/s00134-012-2531-2]

12 **Russell JA**. Bench-to-bedside review: Vasopressin in the management of septic shock. *Crit Care* 2011; **15**: 226 [PMID: 21892977 DOI: 10.1186/cc8224]

13 **Russell JA**. Vasopressor therapy in critically ill patients with shock. *Intensive Care Med* 2019; **45**: 1503-1517 [PMID: 31646370 DOI: 10.1007/s00134-019-05801-z]

14 **Landry DW**, Levin HR, Gallant EM, Ashton RC Jr, Seo S, D'Alessandro D, Oz MC, Oliver JA. Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation* 1997; **95**: 1122-1125 [PMID: 9054839 DOI: 10.1161/01.cir.95.5.1122]

15 **Argenziano M**, Choudhri AF, Oz MC, Rose EA, Smith CR, Landry DW. A prospective randomized trial of arginine vasopressin in the treatment of vasodilatory shock after left ventricular assist device placement. *Circulation* 1997; **96**: II-286 [PMID: 9386112]

16 **Noguera I**, Medina P, Segarra G, Martínez MC, Aldasoro M, Vila JM, Lluch S. Potentiation by vasopressin of adrenergic vasoconstriction in the rat isolated mesenteric artery. *Br J Pharmacol* 1997; **122**: 431-438 [PMID: 9351498 DOI: 10.1038/sj.bjp.0701397]

17 **Treschan TA**, Peters J. The vasopressin system: physiology and clinical strategies. *Anesthesiology* 2006; **105**: 599-612; quiz 639 [PMID: 16931995 DOI: 10.1097/00000542-200609000-00026]

18 **Currigan DA**, Hughes RJ, Wright CE, Angus JA, Soeding PF. Vasoconstrictor responses to vasopressor agents in human pulmonary and radial arteries: an *in vitro* study. *Anesthesiology* 2014; **121**: 930-936 [PMID: 25198173 DOI: 10.1097/ALN.0000000000000430]

19 **Mehta RL**, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A; Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; **11**: R31 [PMID: 17331245 DOI: 10.1186/cc5713]

20 **Sterne JAC**, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366**: l4898 [PMID: 31462531 DOI: 10.1136/bmj.l4898]

21 **Wells G**, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2012 [cited 2020 September 24]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

22 **Higgins JP**, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557-560 [PMID: 12958120 DOI: 10.1136/bmj.327.7414.557]

23 **Cheng Y**, Pan T, Ge M, Chen T, Ye J, Lu L, Chen C, Zong Q, Ding Y, Wang D. Evaluation of Vasopressin for Vasoplegic Shock in Patients With Preoperative Left Ventricular Dysfunction After Cardiac Surgery: A Propensity-Score Analysis. *Shock* 2018; **50**: 519-524 [PMID: 29424795 DOI: 10.1097/SHK.0000000000001114]

24 **Hajjar LA**, Vincent JL, Barbosa Gomes Galas FR, Rhodes A, Landoni G, Osawa EA, Melo RR, Sundin MR, Grande SM, Gaiotto FA, Pomerantzeff PM, Dallan LO, Franco RA, Nakamura RE, Lisboa LA, de Almeida JP, Gerent AM, Souza DH, Gaiane MA, Fukushima JT, Park CL, Zambolim C, Rocha Ferreira GS, Strabelli TM, Fernandes FL, Camara L, Zeferino S, Santos VG, Piccioni MA, Jatene FB, Costa Auler JO Jr, Filho RK. Vasopressin *vs* Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery: The VANCS Randomized Controlled Trial. *Anesthesiology* 2017; **126**: 85-93 [PMID: 27841822 DOI: 10.1097/ALN.0000000000001434]

25 **El Adawy M**, Omran A. Methylene blue *vs* vasopressin in sepsis-induced vasoplegia. *Ain-Shams J Anaesthesiol* 2016; **9**: 319

26 **Nagendran M**, Russell JA, Walley KR, Brett SJ, Perkins GD, Hajjar L, Mason AJ, Ashby D, Gordon AC. Vasopressin in septic shock: an individual patient data meta-analysis of randomised controlled trials. *Intensive Care Med* 2019; **45**: 844-855 [PMID: 31062052 DOI: 10.1007/s00134-019-05620-2]

27 **Gordon AC**, Mason AJ, Thirunavukkarasu N, Perkins GD, Cecconi M, Cepkova M, Pogson DG, Aya HD, Anjum A, Frazier GJ, Santhakumaran S, Ashby D, Brett SJ; VANISH Investigators. Effect of Early Vasopressin *vs* Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. *JAMA* 2016; **316**: 509-518 [PMID: 27483065 DOI: 10.1001/jama.2016.10485]

28 **Russell JA**, Walley KR, Singer J, Gordon AC, Hébert PC, Cooper DJ, Holmes CL, Mehta S, Granton

JT, Storms MM, Cook DJ, Presneill JJ, Ayers D; VASST Investigators. Vasopressin *vs* norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; **358**: 877-887 [PMID: 18305265 DOI: 10.1056/NEJMoa067373]

29 **Hajjar LA**, Zambolim C, Belletti A, de Almeida JP, Gordon AC, Oliveira G, Park CHL, Fukushima JT, Rizk SI, Szeles TF, Dos Santos Neto NC, Filho RK, Galas FRBG, Landoni G. Vasopressin Versus Norepinephrine for the Management of Septic Shock in Cancer Patients: The VANCS II Randomized Clinical Trial. *Crit Care Med* 2019; **47**: 1743-1750 [PMID: 31609774 DOI: 10.1097/CCM.0000000000004023]

30 **Daley MJ**, Lat I, Mieure KD, Jennings HR, Hall JB, Kress JP. A comparison of initial monotherapy with norepinephrine *vs* vasopressin for resuscitation in septic shock. *Ann Pharmacother* 2013; **47**: 301-310 [PMID: 23447481 DOI: 10.1345/aph.1R442]

31 **Luhr R**, Cao Y, Söderquist B, Cajander S. Trends in sepsis mortality over time in randomised sepsis trials: a systematic literature review and meta-analysis of mortality in the control arm, 2002-2016. *Crit Care* 2019; **23**: 241 [PMID: 31269976 DOI: 10.1186/s13054-019-2528-0]

32 **Petros AJ**, Marshall JC, van Saene HK. Should morbidity replace mortality as an endpoint for clinical trials in intensive care? *Lancet* 1995; **345**: 369-371 [PMID: 7772121 DOI: 10.1016/s0140-6736(95)90347-x]

33 **Ospina-Tascón GA**, Büchele GL, Vincent JL. Multicenter, randomized, controlled trials evaluating mortality in intensive care: doomed to fail? *Crit Care Med* 2008; **36**: 1311-1322 [PMID: 18379260 DOI: 10.1097/CCM.0b013e318168ea3e]

34 **Jiang L**, Sheng Y, Feng X, Wu J. The effects and safety of vasopressin receptor agonists in patients with septic shock: a meta-analysis and trial sequential analysis. *Crit Care* 2019; **23**: 91 [PMID: 30871607 DOI: 10.1186/s13054-019-2362-4]

35 **Gaudino M**, Rahouma M, Di Mauro M, Yanagawa B, Abouarab A, Demetres M, Di Franco A, Arisha MJ, Ibrahim DA, Baudo M, Girardi LN, Fremes S. Early Versus Delayed Stroke After Cardiac Surgery: A Systematic Review and Meta-Analysis. *J Am Heart Assoc* 2019; **8**: e012447 [PMID: 31215306 DOI: 10.1161/JAHA.119.012447]

36 **Salazar JD**, Wityk RJ, Grega MA, Borowicz LM, Doty JR, Petrofski JA, Baumgartner WA. Stroke after cardiac surgery: short- and long-term outcomes. *Ann Thorac Surg* 2001; **72**: 1195-201; discussion 1201 [PMID: 11603436 DOI: 10.1016/s0003-4975(01)02929-0]

37 **McIntyre WF**, Um KJ, Alhazzani W, Lengyel AP, Hajjar L, Gordon AC, Lamontagne F, Healey JS, Whitlock RP, Belley-Côté EP. Association of Vasopressin Plus Catecholamine Vasopressors *vs* Catecholamines Alone With Atrial Fibrillation in Patients With Distributive Shock: A Systematic Review and Meta-analysis. *JAMA* 2018; **319**: 1889-1900 [PMID: 29801010 DOI: 10.1001/jama.2018.4528]

38 **Russell JA**, Lee T, Singer J, De Backer D, Annane D. Days alive and free as an alternative to a mortality outcome in pivotal vasopressor and septic shock trials. *J Crit Care* 2018; **47**: 333-337 [PMID: 29958734 DOI: 10.1016/j.jcrc.2018.05.003]

39 **Holmes CL**, Walley KR, Chittock DR, Lehman T, Russell JA. The effects of vasopressin on hemodynamics and renal function in severe septic shock: a case series. *Intensive Care Med* 2001; **27**: 1416-1421 [PMID: 11511958 DOI: 10.1007/s001340101014]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com