ISSN 2220-315x (online)

World Journal of *Experimental Medicine*

World J Exp Med 2022 March 20; 12(2): 16-35

Published by Baishideng Publishing Group Inc

World Journal of Experimental Medicine

Contents

Bimonthly Volume 12 Number 2 March 20, 2022

ORIGINAL ARTICLE

Basic Study

Retrospective Study

World Journal of Experimental Medicine

Bimonthly Volume 12 Number 2 March 20, 2022

Contents

ABOUT COVER

Peer Reviewer of *World Journal of Experimental Medicine*, Mohammed S Razzaque, MBBS, PhD, Professor of Pathology, Lake Erie College of Osteopathic Medicine, 1858 West Grandview Boulevard, Erie, PA 16509, USA. mrazzaque@lecom.edu

AIMS AND SCOPE

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

WJEM mainly publishes articles reporting research results and findings obtained in the field of experimental medicine and covering a wide range of topics including clinical laboratory medicine (applied and basic research in hematology, body fluid examination, cytomorphology, genetic diagnosis of hematological disorders, thrombosis and hemostasis, and blood typing and transfusion), biochemical examination (applied and basic research in laboratory automation and information system, biochemical methodology, and biochemical diagnostics), *etc*.

INDEXING/ABSTRACTING

The *WJEM* is now abstracted and indexed in PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Experimental Medicine

ISSN
ISSN 2220-315x (online)

LAUNCH DATE
December 20, 2011

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Leonardo Roever

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-315x/editorialboard.htm

PUBLICATION DATE
March 20, 2022

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 Experimental Medicine

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

World J Exp Med 2022 March 20; 12(2): 16-25

DOI: 10.5493/wjem.v12.i2.16

ISSN 2220-315x (online)

ORIGINAL ARTICLE

Basic Study

Machine learning algorithm using publicly available echo database for simplified "visual estimation" of left ventricular ejection fraction

Michael Blaivas, Laura Blaivas

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Cabezuelo AS, United States; Muneer A, United States

Received: October 11, 2021
Peer-review started: October 11, 2021
First decision: December 9, 2021
Revised: December 14, 2021
Accepted: March 6, 2022
Article in press: March 6, 2022
Published online: March 20, 2022

Michael Blaivas, Department of Medicine, University of South Carolina School of Medicine, Roswell, GA 30076, United States

Laura Blaivas, Department of Environmental Science, Michigan State University, Roswell, Georgia 30076, United States

Corresponding author: Michael Blaivas, MD, Attending Doctor, Professor, Department of Medicine, University of South Carolina School of Medicine, PO Box 769209, Roswell, GA 30076, United States. mike@blaivas.org

Abstract

BACKGROUND

Left ventricular ejection fraction calculation automation typically requires complex algorithms and is dependent of optimal visualization and tracing of endocardial borders. This significantly limits usability in bedside clinical applications, where ultrasound automation is needed most.

AIM

To create a simple deep learning (DL) regression-type algorithm to visually estimate left ventricular (LV) ejection fraction (EF) from a public database of actual patient echo examinations and compare results to echocardiography laboratory EF calculations.

METHODS

A simple DL architecture previously proven to perform well on ultrasound image analysis, VGG16, was utilized as a base architecture running within a long short term memory algorithm for sequential image (video) analysis. After obtaining permission to use the Stanford EchoNet-Dynamic database, researchers randomly removed approximately 15% of the approximately 10036 echo apical 4-chamber videos for later performance testing. All database echo examinations were read as part of comprehensive echocardiography study performance and were coupled with EF, end systolic and diastolic volumes, key frames and coordinates for LV endocardial tracing in csv file. To better reflect point-of-care ultrasound (POCUS) clinical settings and time pressure, the algorithm was trained on echo video correlated with calculated ejection fraction without incorporating additional volume, measurement and coordinate data. Seventy percent of the original data was used for algorithm training and 15% for validation during training. The previously randomly separated 15% (1263 echo videos) was used for algorithm

performance testing after training completion. Given the inherent variability of echo EF measurement and field standards for evaluating algorithm accuracy, mean absolute error (MAE) and root mean square error (RMSE) calculations were made on algorithm EF results compared to Echo Lab calculated EF. Bland-Atlman calculation was also performed. MAE for skilled echocardiographers has been established to range from 4% to 5%.

RESULTS
The DL algorithm visually estimated EF had a MAE of 8.08% (95%CI 7.60 to 8.55) suggesting good performance compared to highly skill humans. The RMSE was 11.98 and correlation of 0.348.

CONCLUSION
This experimental simplified DL algorithm showed promise and proved reasonably accurate at visually estimating LV EF from short real time echo video clips. Less burdensome than complex DL approaches used for EF calculation, such an approach may be more optimal for POCUS settings once improved upon by future research and development.

Key Words: Deep learning; Artificial intelligence; Point-of-care-ultrasound; Ejection fraction; Cardiac; Echocardiography

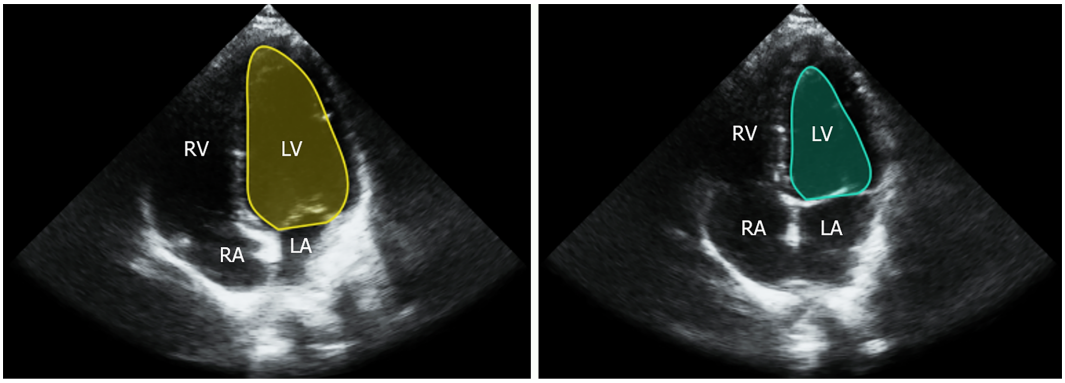
Core Tip: The manuscript describes a novel study of machine learning algorithm creation for point of care ultrasound left ventricular ejection fraction estimation without measurements or modified Simpson's Rule calculations typically seen in artificial applications designed to calculate the left ventricular ejection fraction. I believe the manuscript will be of interest to your readers and significantly add to the body of literature related to bedside clinical ultrasound artificial intelligence applications.

Citation: Blaivas M, Blaivas L. Machine learning algorithm using publicly available echo database for simplified "visual estimation" of left ventricular ejection fraction. *World J Exp Med* 2022; 12(2): 16-25
URL: https://www.wjgnet.com/2220-315x/full/v12/i2/16.htm
DOI: https://dx.doi.org/10.5493/wjem.v12.i2.16

INTRODUCTION

Left ventricular (LV) ejection fraction (EF) calculation is the most common method for quantifying left ventricular systolic function[1,2]. Not only is EF the most widely used measure of cardiac function in clinical care but it is especially important in severely ill and unstable patients. In critically ill patients, rapidly obtaining the EF helps narrow treatment options and can identify possible causes behind unstable vital signs. EF can be assessed using a variety of imaging modalities and methods. Magnetic resonance imaging, while providing high accuracy, is logistically difficult to perform in most urgent or emergent situations[3,4]. The resultant effective criterion standard is EF calculation by comprehensive 2-D echocardiography, typically using the modified Simpson's rule[5]. However, despite ultrasound's lower cost and greater accessibility than MRI, and the potential for bedside imaging by an echocardiography tech, results are typically delayed by hours to days after examination performance. This "results time lag" is impractical in any clinical scenario requiring rapid patient assessment and decision making [6].

The modified Simpson's approach uses a mathematical approach for estimating volumes, based on LV images in two orthogonal planes[7]. The operator carefully outlines endocardial borders for end systolic and end diastolic frames in both planes (Figure 1). Using a single plane, typically from the apical 4 chamber view, is possible, but leads to lower accuracy when compared to a two plane approach [8]. Manually calculating EF using ultrasound is time consuming, requires considerable training and expertise and is rarely performed, even by highly experienced providers, in POCUS settings due to hardware and time limitations[9]. An alternative method is visual estimation by the operator. Experienced echocardiography technologists and cardiologists specializing in echocardiography can visually estimate EF with reasonable accuracy[10]. However, rank and file POCUS users are only able to grade EF visually into broad general categories such as normal, moderately and severely depressed. This level of gradation equates to just three 20% EF ranges while most echocardiography laboratories report EF in much more granular 5% ranges between 10% to 70%[11].



DOI: 10.5493/wjem.v12.i2.16

Figure 1 The operator carefully outlines endocardial borders for end systolic and end diastolic frames in both planes. RV: Right Ventricle; RA: Right Atrium; LV: Left Ventricle; LA: Left Atrium.

Although visual EF estimation is indeed faster and theoretically better suited for many acute care scenarios, it has to be accurate and precise enough to detect clinically relevant changes and be repeatable. Given that human operator visual estimation is highly subjective, reproducibility in a high pressure clinical setting such as with a critically ill patient undergoing interventions and resuscitation, can be especially difficult[12]. The challenge can be made even more difficult if the operator obtaining the visual EF estimation changes, such as with shift change or transition of care. The decompensating patient, now being treated by a new provider, may not have an objective and reproducible EF assessment for comparison. In such cases especially, a more objective, precise and reproducible, yet rapid, measure is highly desirable.

Considerable work has occurred with Artificial Intelligence (AI) in automatic EF estimation in the academic research space as well as some with commercial ventures, resulting in several hardware/software products available for purchase and use by clinicians[13-16]. Liu *et al*[16] developed a DPS-Net based algorithm using a biplane Simpson's rule for EF determination. The investigators achieved high correlation with gold standard testing based on receiver operator curves approaching 0.974. However, accurate segmentation of the LV in the apical 4 and 2 chamber planes, for both end systole and end diastole. This method, while accurate is computationally intensive and would require POCUS users to obtain an imaging plane they are rare trained to achieve (apical 2 chamber). Strezecka *et al*[13] studied automated EF measurement specifically on a POCUS device, which would inherently indicate use by clinicians with little training in echo. The researchers used an algorithm capable of EF determination from just one imaging plane, the apical 4 chamber view. However, they depicted several failures of the algorithm to detect and trace the endocardial border, a critical step in their EF calculation method. Unfortunately, POCUS settings often result in images with limited endocardial border detail, which can lead to the failure of such algorithms on a regular basis. To date, the majority of the commercial products utilize some form of a modified Simpson's rule approach and depend significantly on clear images with well delineated endocardial borders[17,18]. In fact, the challenge of determining an EF in the POCUS setting with POCUS equipment has already led to one class 2 FDA recall and another vendor's EF application removal from the market and requirement for full FDA review[19].

In order to explore improved visual EF estimation, researchers sought to create a simple deep learning (DL) algorithm to rapidly "visually" estimate EF from a public database of actual patient echo examinations and compare results to echocardiography laboratory EF calculations.

MATERIALS AND METHODS

Study design

Researchers utilized simple DL architecture previously found to perform well in ultrasound image analysis. The VGG16 architecture was used as a base to run inside a long short term memory (LSTM) algorithm for video analysis by sequential frames. To better reflect POCUS clinical settings and time pressure, the algorithm was trained on echo videos correlated with calculated ejection fraction without incorporating additional available measurement data such as end systolic and diastolic volumes, key frames or endocardial border coordinates, from a large public echo database. Seventy percent of the data was used for algorithm training and 15% for validation during training. A previously separated 15% was reserved for algorithm performance testing. Algorithm training was optimized through variably adjusting batch size, number of epochs (an epoch is one round of DL algorithm training through all of the data), learning rate and the number of frames the LSTM analyses at once. A total of 1263 randomly selected echo videos were used to test algorithm performance. For final DL testing,

researchers created a script to generate a CSV file containing a calculation of difference between algorithm estimated EF and criterion standard EF calculation for each video along with a cumulative average. The study did not utilize any patient data nor medical center facilities or resources and was exempted from Institutional Review Board (IRB) review.

Study data

Researchers were granted permission to access the Stanford EchoNet-Dynamic database after submitting an application to the data curators of the approximately 10036 apical 4-chamber (A4C) echo A4C video repository[20]. After downloading the video data and corresponding spreadsheet, researchers randomly removed approximately 15% (1263 A4C) of the A4C videos for final performance testing. Stanford researchers created the EchoNet-Dynamic database "to provide images to study cardiac motion and chamber volumes using echocardiography, or cardiac ultrasound, videos obtained in real clinical practice for diagnosis and medical decision making[20]." Data contained in the database is depicted in Table 1. All extracted Stanford de-identified echo examination data contained EF, end systolic and diastolic volumes, key frames and coordinates for LV endocardial tracing and were read as part of comprehensive echocardiography study performance. A4C videos were 112 × 112 pixels in size, compared to typical exported examination videos which can be 1024 × 560 pixels in size, or larger (Figure 2). Many of these videos were noted to have noisy images impacting LV endocardial delineation.

Algorithm design

The publicly available Keras-based (a python machine learning library) VGG-16 bidirectional LSTM DL algorithm, which had produced superior performance in prior studies, was chosen for this project[21]. Researchers coded the DL algorithm in the Python programming language version 3.72. VGG-16 convolutional neural network (CNN) architecture is obtainable from public sources including an online repository, github.com. VGG is a rudimentary CNN containing only 16 Layers, in comparison to most modern CNNs which are made of hundreds of layers. Previous work suggests simpler CNNs like VGG-16 may perform better than larger complex ones in classifying some grayscale ultrasound images[21].

The VGG-16 CNN was used inside a Long Short Term Memory algorithm. A LSTM network is one of several approaches geared for video analysis by having the VGG-16 CNN analyze each frame sequentially. On top of the VGG-16 functionality the LSTM tracks temporal changes which may occur from one frame to the next. For studies with large dynamic components such as lung ultrasound applications and echocardiography, such approaches are especially critical. Standard LSTM networks are designed to track temporal changes in one direction. Researchers chose a bidirectional LSTM architecture for even better performance. Bi-directional LSTM allows temporal information to flow in both directions, forward and reverse, resulting in higher sensitivity and specificity for detecting change from one frame to another. Higher sensitivity and specificity result from the bi-directional LSTM's enhanced understanding of what context motion or change occurs in. Researchers used standard VGG-16 specific initial training weights for the VGG-16 bidirectional LSTM. Weights used in a CNN are best viewed as learnable mathematical parameters. These weights are used by a CNN to analyze image features and through that the entire image, leading to image classification or object detection.

The bidirectional LSTM was trained on 70% of the original downloaded data. Stepwise adjustments were made to optimizers, batch size and learning rates in response to training results. Total epochs were also manipulated training to improve results for highest accuracy.

Algorithm validation and testing

LSTM architecture and coding included scripts for automatic cross validation during each epoch automatically. Additionally, researchers added code to automatically calculate a running MAE from epoch to epoch in order to provide additional training performance clues. After results were optimized and no further adjustments improved performance, the algorithm was tested on the 1263 apical 4 chamber echocardiograph videos randomly selected and set aside upon original data download from EchoNet. These randomly selected video EFs ranged from 7% to 91%. During this final testing phase, researchers again coded the algorithm to produce an MAE and also a running CSV file with each CNN predicted EF and the actual calculated EF made at Stanford using the modified Simpson's rule.

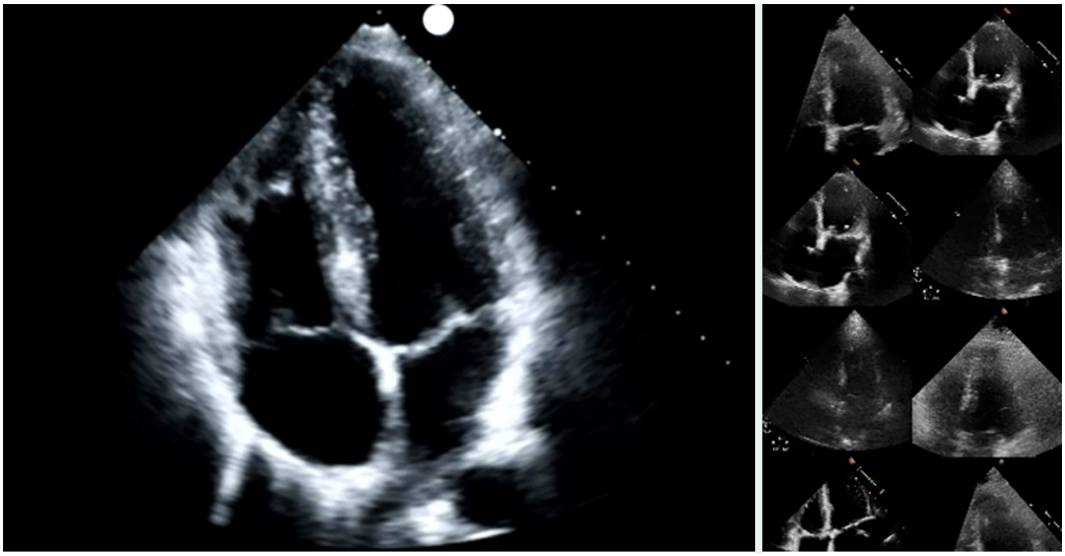
Statistical analysis

Echocardiographic EF measurements inherently vary in the same subject due to both patient and operator factors[21]. Therefore, exact agreement between the calculated EF and LSTM prediction are seen as unlikely. Thus, mean absolute error (MAE) and root mean square error (RMSE) calculations were performed on algorithm EF results, in keeping with field standards, to evaluate relative algorithm accuracy compared to Echo Lab calculated EF[21]. MAE for highly skilled echocardiographers has been established to range from 4 to 5%[22]. A highly complex DL algorithm using additional data points and built by database creators achieved a MAE of 5.44% with the same videos[20]. Researchers also performed Bland-Altman analysis between comprehensive echocardiography laboratory bi-planar modified Simpson's rule EF results and the visual estimations by the DL algorithm. Statistical analyses

Table 1 EchoNet-dynamic database contents

Category	Content in Category
Video file name	File name linked to annotations, labels and videos
Subject age	Scanning subjects age reported in years
Subject gender	Scanning subject gender
Ejection fraction	EF calculated through a ratio of ESV and EDV
End systolic volume	ESV calculated using a method of discs during the echocardiogram
End diastolic volume	EDV calculated using a method of discs during the echocardiogram
Height of video frame	Individual frame height for the echo videos
Width of video frame	Individual frame width for the echo videos
Frames per second	FPS rate for the echo video
Number of frames	Number of frames in the entire echo video
Split from benchmark	Split of videos into train/validate and test datasets from original work

ESV: End systolic volume; EDV: End diastolic volume; EF: Ejection fraction of the left ventricle; FPS: Frames per second.



DOI: 10.5493/wjem.v12.i2.16

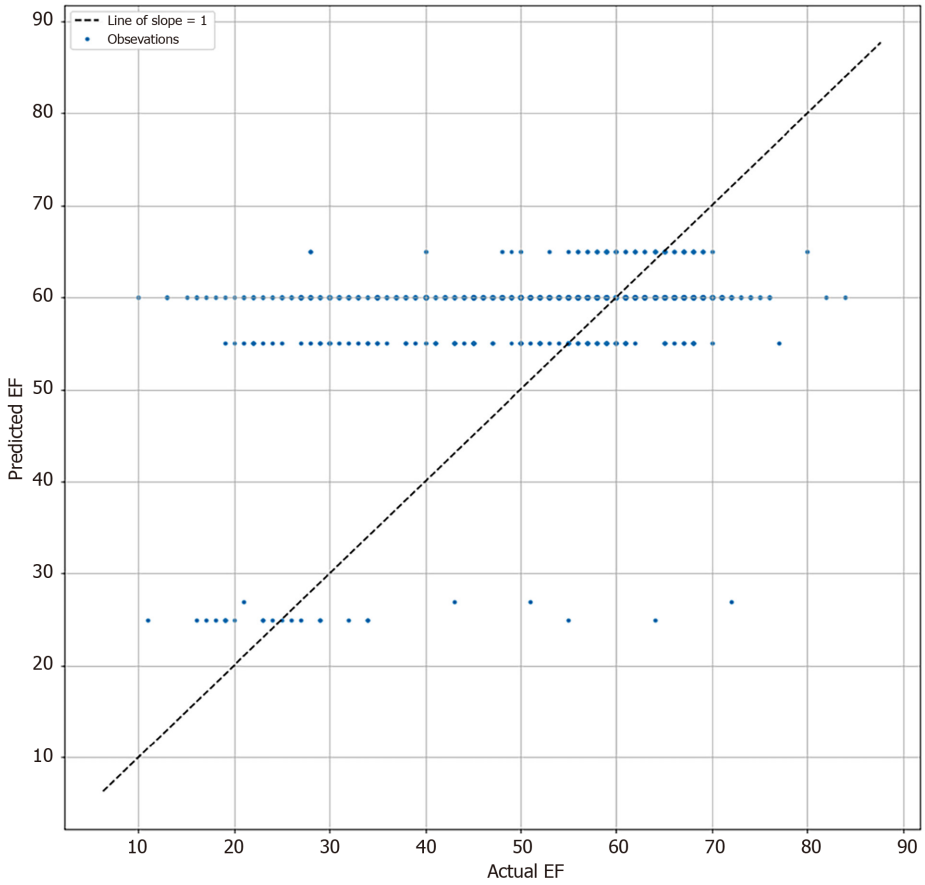
Figure 2 Apical 4-chamber videos were 112 × 112 pixels in size, compared to typical exported examination videos which can be 1024 × 560 pixels in size, or larger.

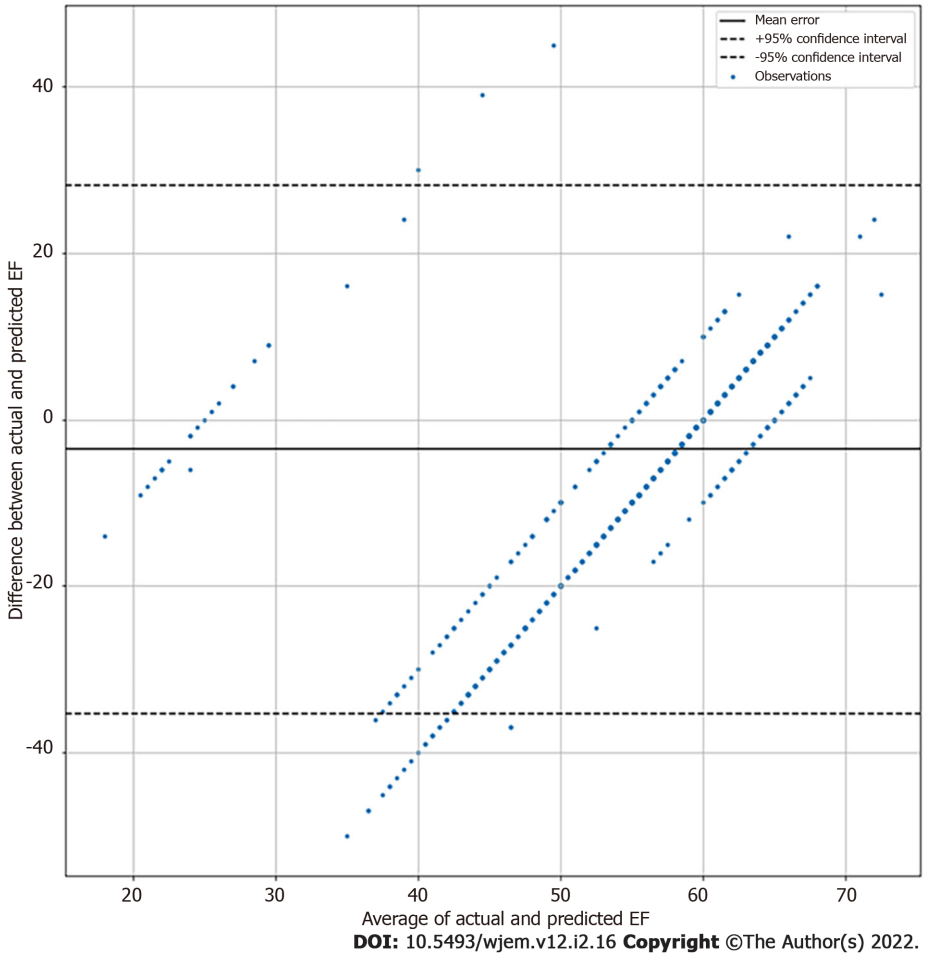
were performed using Python Scripts.

RESULTS

The LSTM DL algorithm using original greyscale video for visual EF estimation resulted in a MAE of 8.08% (95%CI 7.60 to 8.55) when tested on 1263 apical 4 chamber videos previously unseen by the algorithm. This suggests good performance compared to highly skilled human operators such as echo technologists or echo trained cardiologists who typically have an MAE of 4% to 5%[22]. The RMSE was 11.98 and correlation of 0.348. The standard deviation was 8.58%. The Bland-Altman plots are shown in Figure 3. For reference, the DynamicEcho creators tested 9 different DL models obtaining a best MAE of 5.44 and worst of 51.8. RMSE ranged similarly from 6.16 to 35.2, respectively[20]. Human experts tested by DynamicEcho creators achieved an MAE of 3.12 and RMSE of 4.57[20].

Best results were obtained with an LSTM frame analysis of 50, 40 epochs, batch size of 40, using an Adam optimizer and batch size of 10 videos. The DL was able to analyze and interpret reach of the 1263 test videos with no failures, Training failed on three videos which were found to be corrupted (not





DOI: 10.5493/wjem.v12.i2.16

Figure 3 The Bland-Altman plots. EF: Ejection fraction.

previously identified) and contained no usable data.

DISCUSSION

This simple DL algorithm proved fairly accurate in delivering visual EF predictions when tested on 1263 actual patient A4C echocardiogram videos and compared to comprehensive cardiac laboratory echocardiography EF calculations. Further, its agreement as measured by MAE was within three percentage points of what is expected from expert echocardiographers and approximately two percentage points of the best performing complex algorithm designed by the DynamicEcho database creators. utilizing additional available data points. The creation of "visual" EF estimation DL algorithms has been overlooked to date by POCUS machine vendors, but considerable potential exists for its implementation.

Emergent situations such as unstable vital signs require rapid patient assessment. Simple measurements like blood pressure, heart rate and oxygen saturations are useful initial parameters, yet clinicians may require more information than vital signs provide. Perhaps the most important general information in many emergent medical situations is assessment of systolic cardiac function. Uncovering abnormal cardiac function is immensely informative to the clinician, especially when it was previously unknown. An unstable patient with normal cardiac function can tolerate interventions that are contraindicated for those with decreased EF, such as immediate administration of fluid boluses. Alternatively, severely depressed systolic cardiac function may lead the clinician directly to pharmacological intervention with centrally administered vasopressors to increase blood pressure and systemic perfusion. Unfortunately, without actually imaging the heart in real time at bedside, clinicians have few options for dividing current systolic function reliably. POCUS cardiac imaging is the most accessible imaging solution worldwide and may hold the answer for emergent assessment even in the hands of novice users[23].

POCUS literature on cardiac function assessment dates back nearly 30 years, and has ranged from simply identifying cardiac activity in arresting patients to identification of tamponade and even visual assessment of EF[24,25,11]. One early study showed that POCUS users, who received focused training on visual EF estimation, could successfully categorize EF into normal, moderately and severely depressed categories[11]. This equates to approximately 20% categories given a typically EF range of 10% on the low side and 70% on the high. In contrast, a report obtained from a echocardiography laboratory will have an EF presented as a 5% range. While knowing if the EF is normal, moderately or severely depressed can be helpful in some clinical situations, a more granular measure and one that is reproducible would be necessary in others. For instance such as a patient whose EF has dropped from 50% to 40% or from 35% to 25%. Both may represent critically important changes as one shows a 10% decrease from a near normal EF and the other a deterioration from a poor EF to significantly worse. Additionally, stressful situations such as emergency scenarios may result in a confidence drop in measurement repeatability and a change of the provider visually estimating the EF can lead more inter-observer problems with identifying EF changes[26]. A precise and repeatable EF measurement tool would optimally be available at very patient's bedside, but in reality most clinicians still do not use ultrasound at all, and among those that do the vast majority cannot perform modified Simpson's rule calculation from the apical 4 and 2 chamber views[27]. Similarly, most clinicians still lack the experience to reliably visually estimate the EF such as a highly seasoned cardiologist or echo tech.

EF calculation *via* echo with AI has been well explored by large research groups with good results, but often complex algorithms and some requiring multiple steps[28,29]. The creators of the Stanford EchoNet-Dynamic database were successful in creating several algorithms with the best one performing on par with echo techs in a comprehensive echocardiography laboratory[19]. Not surprisingly, commercial vendors of AI technology have finally turned their attention to the POCUS market and its needs. One of the first applications focused on by a number of both hardware/software and software only vendors has been EF calculation. Most utilize a modified Simpson's rule approach requiring good imaging planes and in some cases acquisition of a 2 chamber apical view. Typically the internal LV tracing made by the software are displayed and the clinician is asked to adjust them as needed, something beyond the skill level of most POCUS users.

This is the first POCUS research effort without involvement of a commercial entity and using a classical modified Simpson's rule approach that could be identified in the literature. It suggests that rapid visual EF estimation may be feasible as a clinical DL tool for emergent clinical settings. The MAE of 8%, while not as good as attained by expert echocardiographers still shows significant potential for such deep learning algorithms. The original DynamicEcho creators attained a range of MAEs for multiple DL algorithm approaches using additional data beside simple video analysis. The highest MAE was over 50% and best performing at 5.44% further validating this initial effort as a worthwhile development pathway for future DL solutions. No doubt future developers, using higher resolution videos could greatly improve on these results, especially prior to putting them into commercially available software. The visual estimation DL algorithm described here using LSTM can run in real time on an ultrasound device while a novice POCUS user is imaging the heart. The ability to estimate EF in

real time, without need for a pause while the ultrasound machine runs the DL algorithm tracing endocardial borders and comparing end systolic and end diastolic volumes, should improve clinicians' abilities for rapid medical decision making.

Our study had multiple limitations. The database contained a large number of videos with comprehensive echocardiography laboratory calculated EF, but the videos to which access was provided were very small at 112 × 112 pixels, potentially limited algorithm performance. While DL algorithms often resize video during training in order to decrease computational burden on the algorithm, researchers have seen improved results when using larger image size, double or triple the provided frame dimension, when training on ultrasound video. Although the DL algorithm was tested on a large number of echo videos covering the broad range of EFs from very low to high, this is not the same as actual implementation of an algorithm on a POCUS device in a clinical setting to test its performance. The steps necessary to achieve that were outside the scope of our study, but are technically, if not logistically simple. Additionally, the source videos were typically from one of a handful of ultrasound machines, thus likely leading to a less robust algorithm as recent work show the potential for significant DL algorithm performance degradation even when faced with superior image quality videos and near total performance failure when significantly inferior image quality videos are faced by the algorithm [30]. Another source of disagreement with comprehensive echo lab EF calculation and our DL algorithm lie in our use of only 4 chamber videos (the only ones available for download). The optimal approach to EF calculation is using the ESV and EDV volume of the left ventricle in both apical 4 chamber and apical 2 chamber views. This results in a more accurate EF calculation and should naturally explain some of the differences found[7].

CONCLUSION

This simplified DL algorithm proved fairly accurate at visually estimating LV EF from short real time echo video clips. It opens up an exploratory avenue that differs from most current commercial applications seen in automated EF calculations. Less burdensome than complex DL approaches used for EF calculation, such an approach may be more optimal for POCUS settings. Future research lines should explore actual on the edge implementation and testing in different clinical environments. Additionally, an exploration of a more diverse database with multiple ultrasound machines represented as well as higher quality videos should be undertaken to further implore potential accuracy improvements in visual EF estimation.

ARTICLE HIGHLIGHTS

Research background

Deep learning has been explored in medical ultrasound image analysis for several years and some applications have focused on evaluation of cardiac function. To date, most academic research and commercial deep learning ventures to automate left ventricular ejection calculation have resulted in image quality dependent highly complex algorithms which require multiple views from the apical window. Research into alternative approaches have been limited.

Research motivation

To explore a deep learning approach modeling visual ejection fraction estimation, thereby modeling the approach taken by highly skill electrocardiographers with decades of experience. If possible, such an approach could work with less than ideal images and be less computationally burdensome, both ideal for point of care ultrasound applications, where experts are unlikely to be present.

Research objectives

To develop a deep learning algorithm capable of visual estimation of left ventricular ejection fraction.

Research methods

Long short term memory structure using a VGG16 convolutional neural network capable of bidirectionality was employed for video analysis of cardiac function. The algorithm was trained on a publicly available echo database with ejection fraction calculations made at a comprehensive echocardiography laboratory. After training, the algorithm was tested on a data subset specifically set aside prior to training.

Research results

The algorithm performed well in comparison to baseline data for correlation between echocardiographers calculating ejection fraction and gold standards. It outperformed some previously published

algorithms for agreement.

Research conclusions

Deep learning based visual ejection fraction estimation is feasible and could be improved with further refinement and higher quality databases.

Research perspectives

Further research is needed to explore the impact of higher quality video for training and with a more diverse ultrasound machine source.

FOOTNOTES

Author contributions: Blaivas M contributed ultrasound data; Blaivas M and Blaivas L designed the research, sorted, cleaned ultrasound data, designed deep learning architecture, trained the algorithm, performed statistical analysis using Python scripts and wrote the manuscript; Blaivas L performed coding in Python computer language.

Institutional review board statement: Completed, see previously uploaded document.

Conflict-of-interest statement: Blaivas M consults for Anavasi Diagnostics, EthosMedical, HERO Medical and Sonosim.

Data sharing statement: Data was acquired from a public database following approval of application and is available to researchers from the source.

Country/Territory of origin: United States

ORCID number: Michael Blaivas 0000-0001-7196-9765; Laura Blaivas 0000-0002-0057-005X.

S-Editor: Wang LL
L-Editor: A
P-Editor: Li X

REFERENCES

1 **Halliday BP**, Senior R, Pennell DJ. Assessing left ventricular systolic function: from ejection fraction to strain analysis. *Eur Heart J* 2021; **42**: 789-797 [PMID: 32974648 DOI: 10.1093/eurheartj/ehaa587]
2 **Kusunose K**, Zheng R, Yamada H, Sata M. How to standardize the measurement of left ventricular ejection fraction. *J Med Ultrason (2001)* 2022; **49**: 35-43 [PMID: 34322777 DOI: 10.1007/s10396-021-01116-z]
3 **O'Quinn R**, Ferrari VA, Daly R, Hundley G, Baldassarre LA, Han Y, Barac A, Arnold A. Cardiac Magnetic Resonance in Cardio-Oncology: Advantages, Importance of Expediency, and Considerations to Navigate Pre-Authorization. *JACC CardioOncol* 2021; **3**: 191-200 [PMID: 34396324 DOI: 10.1016/j.jaccao.2021.04.011]
4 **Vega-Adauy J**, Tok OO, Celik A, Barutcu A, Vannan MA. Comprehensive Assessment of Heart Failure with Preserved Ejection Fraction Using Cardiac MRI. *Heart Fail Clin* 2021; **17**: 447-462 [PMID: 34051976 DOI: 10.1016/j.hfc.2021.03.006]
5 **Sanna GD**, Canonico ME, Santoro C, Esposito R, Masia SL, Galderisi M, Parodi G, Nihoyannopoulos P. Echocardiographic Longitudinal Strain Analysis in Heart Failure: Real Usefulness for Clinical Management Beyond Diagnostic Value and Prognostic Correlations? *Curr Heart Fail Rep* 2021; **18**: 290-303 [PMID: 34398411 DOI: 10.1007/s11897-021-00530-1]
6 **Vieillard-Baron A**, Millington SJ, Sanfilippo F, Chew M, Diaz-Gomez J, McLean A, Pinsky MR, Pulido J, Mayo P, Fletcher N. A decade of progress in critical care echocardiography: a narrative review. *Intensive Care Med* 2019; **45**: 770-788 [PMID: 30911808 DOI: 10.1007/s00134-019-05604-2]
7 **Nosir YF**, Vletter WB, Boersma E, Frowijn R, Ten Cate FJ, Fioretti PM, Roelandt JR. The apical long-axis rather than the two-chamber view should be used in combination with the four-chamber view for accurate assessment of left ventricular volumes and function. *Eur Heart J* 1997; **18**: 1175-1185 [PMID: 9243153 DOI: 10.1093/oxfordjournals.eurheartj.a015414]
8 **Kuroda T**, Seward JB, Rumberger JA, Yanagi H, Tajik AJ. Left ventricular volume and mass: Comparative study of two-dimensional echocardiography and ultrafast computed tomography. *Echocardiography* 1994; **11**: 1-9 [PMID: 10150561 DOI: 10.1111/j.1540-8175.1994.tb01040.x]
9 **Jafari MH**, Girgis H, Van Woudenberg N, Liao Z, Rohling R, Gin K, Abolmaesumi P, Tsang T. Automatic biplane left

ventricular ejection fraction estimation with mobile point-of-care ultrasound using multi-task learning and adversarial training. *Int J Comput Assist Radiol Surg* 2019; **14**: 1027-1037 [PMID: 30941679 DOI: 10.1007/s11548-019-01954-w]

10 **Gudmundsson P**, Rydberg E, Winter R, Willenheimer R. Visually estimated left ventricular ejection fraction by echocardiography is closely correlated with formal quantitative methods. *Int J Cardiol* 2005; **101**: 209-212 [PMID: 15882665 DOI: 10.1016/j.ijcard.2004.03.027]

11 **Moore CL**, Rose GA, Tayal VS, Sullivan DM, Arrowood JA, Kline JA. Determination of left ventricular function by emergency physician echocardiography of hypotensive patients. *Acad Emerg Med* 2002; **9**: 186-193 [PMID: 11874773 DOI: 10.1111/j.1553-2712.2002.tb00242.x]

12 **Etherington N**, Larrigan S, Liu H, Wu M, Sullivan KJ, Jung J, Boet S. Measuring the teamwork performance of operating room teams: a systematic review of assessment tools and their measurement properties. *J Interprof Care* 2021; **35**: 37-45 [PMID: 31865827 DOI: 10.1080/13561820.2019.1702931]

13 **Filipiak-Strzecka D**, Kasprzak JD, Wejner-Mik P, Szymczyk E, Wdowiak-Okrojek K, Lipiec P. Artificial Intelligence-Powered Measurement of Left Ventricular Ejection Fraction Using a Handheld Ultrasound Device. *Ultrasound Med Biol* 2021; **47**: 1120-1125 [PMID: 33451814 DOI: 10.1016/j.ultrasmedbio.2020.12.003]

14 **Aldaas OM**, Igata S, Raisinghani A, Kraushaar M, DeMaria AN. Accuracy of left ventricular ejection fraction determined by automated analysis of handheld echocardiograms: A comparison of experienced and novice examiners. *Echocardiography* 2019; **36**: 2145-2151 [PMID: 31786824 DOI: 10.1111/echo.14546]

15 **Narang A**, Bae R, Hong H, Thomas Y, Surette S, Cadieu C, Chaudhry A, Martin RP, McCarthy PM, Rubenson DS, Goldstein S, Little SH, Lang RM, Weissman NJ, Thomas JD. Utility of a Deep-Learning Algorithm to Guide Novices to Acquire Echocardiograms for Limited Diagnostic Use. *JAMA Cardiol* 2021; **6**: 624-632 [PMID: 33599681 DOI: 10.1001/jamacardio.2021.0185]

16 **Liu X**, Fan Y, Li S, Chen M, Li M, Hau WK, Zhang H, Xu L, Lee AP. Deep learning-based automated left ventricular ejection fraction assessment using 2-D echocardiography. *Am J Physiol Heart Circ Physiol* 2021; **321**: H390-H399 [PMID: 34170197 DOI: 10.1152/ajpheart.00416.2020]

17 **Yoon YE**, Kim S, Chang HJ. Artificial Intelligence and Echocardiography. *J Cardiovasc Imaging* 2021; **29**: 193-204 [PMID: 34080347 DOI: 10.4250/jcvi.2021.0039]

18 **Guppy-Coles KB**, Prasad SB, Smith KC, Lo A, Beard P, Ng A, Atherton JJ. Accuracy of Cardiac Nurse Acquired and Measured Three-Dimensional Echocardiographic Left Ventricular Ejection Fraction: Comparison to Echosonographer. *Heart Lung Circ* 2020; **29**: 703-709 [PMID: 31320256 DOI: 10.1016/j.hlc.2019.04.008]

19 **U.S. Food and Drug Administration**. [cited 20 July 2021]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRes/res.cfm?ID=173162

20 **Ouyang D**, He B, Ghorbani A, Lungren M, Ashley E, Liang D, Zou J. EchoNet-Dynamic: a Large New Cardiac Motion Video Data Resource for Medical Machine Learning. 33rd Conference on Neural Information Processing Systems (NeurIPS 2019), 2019: 1-11

21 **Blaivas M**, Blaivas L. Are All Deep Learning Architectures Alike for Point-of-Care Ultrasound? *J Ultrasound Med* 2020; **39**: 1187-1194 [PMID: 31872477 DOI: 10.1002/jum.15206]

22 **Farsalinos KE**, Daraban AM, Ünlü S, Thomas JD, Badano LP, Voigt JU. Head-to-Head Comparison of Global Longitudinal Strain Measurements among Nine Different Vendors: The EACVI/ASE Inter-Vendor Comparison Study. *J Am Soc Echocardiogr* 2015; **28**: 1171-1181, e2 [PMID: 26209911 DOI: 10.1016/j.echo.2015.06.011]

23 **Maw AM**, Galvin B, Henri R, Yao M, Exame B, Fleshner M, Fort MP, Morris MA. Stakeholder Perceptions of Point-of-Care Ultrasound Implementation in Resource-Limited Settings. *Diagnostics (Basel)* 2019; **9** [PMID: 31635219 DOI: 10.3390/diagnostics9040153]

24 **Blaivas M**, Fox JC. Outcome in cardiac arrest patients found to have cardiac standstill on the bedside emergency department echocardiogram. *Acad Emerg Med* 2001; **8**: 616-621 [PMID: 11388936 DOI: 10.1111/j.1553-2712.2001.tb00174.x]

25 **Plummer D**, Brunette D, Asinger R, Ruiz E. Emergency department echocardiography improves outcome in penetrating cardiac injury. *Ann Emerg Med* 1992; **21**: 709-712 [PMID: 1590612 DOI: 10.1016/s0196-0644(05)82784-2]

26 **Al-Ghareeb A**, McKenna L, Cooper S. The influence of anxiety on student nurse performance in a simulated clinical setting: A mixed methods design. *Int J Nurs Stud* 2019; **98**: 57-66 [PMID: 31284161 DOI: 10.1016/j.ijnurstu.2019.06.006]

27 **Pouryahya P**, McR Meyer AD, Koo MPM. Prevalence and utility of point-of-care ultrasound in the emergency department: A prospective observational study. *Australas J Ultrasound Med* 2019; **22**: 273-278 [PMID: 34760569 DOI: 10.1002/ajum.12172]

28 **Kim T**, Hedayat M, Vaitkus VV, Belohlavek M, Krishnamurthy V, Borazjani I. Automatic segmentation of the left ventricle in echocardiographic images using convolutional neural networks. *Quant Imaging Med Surg* 2021; **11**: 1763-1781 [PMID: 33936963 DOI: 10.21037/qims-20-745]

29 **Asch FM**, Mor-Avi V, Rubenson D, Goldstein S, Saric M, Mikati I, Surette S, Chaudhry A, Poilvert N, Hong H, Horowitz R, Park D, Diaz-Gomez JL, Boesch B, Nikravan S, Liu RB, Philips C, Thomas JD, Martin RP, Lang RM. Deep Learning-Based Automated Echocardiographic Quantification of Left Ventricular Ejection Fraction: A Point-of-Care Solution. *Circ Cardiovasc Imaging* 2021; **14**: e012293 [PMID: 34126754 DOI: 10.1161/CIRCIMAGING.120.012293]

30 **Blaivas M**, Blaivas LN, Tsung JW. Deep Learning Pitfall: Impact of Novel Ultrasound Equipment Introduction on Algorithm Performance and the Realities of Domain Adaptation. *J Ultrasound Med* 2021 [PMID: 34133034 DOI: 10.1002/jum.15765]

World Journal of Experimental Medicine

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

World J Exp Med 2022 March 20; 12(2): 26-35

DOI: 10.5493/wjem.v12.i2.26

ISSN 2220-315x (online)

ORIGINAL ARTICLE

Retrospective Study

Comparison between SARS-CoV-2 positive and negative pneumonia in children: A retrospective analysis at the beginning of the pandemic

Adil Zhamankulov, Rafail Rozenson, Marina Morenko, Ulzhan Akhmetova, Alina Tyo, Dimitri Poddighe

Specialty type: Infectious diseases

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Arumugam VA, India; Bersot CD, Brazil

Received: October 30, 2021
Peer-review started: October 30, 2021
First decision: December 27, 2021
Revised: December 29, 2021
Accepted: February 27, 2022
Article in press: February 27, 2022
Published online: March 20, 2022

Adil Zhamankulov, Rafail Rozenson, Marina Morenko, Ulzhan Akhmetova, Alina Tyo, Department of Children's diseases, Astana Medical University, First Children's Municipal Hospital, Nur-Sultan 010000, Kazakhstan

Dimitri Poddighe, Clinical Academic Department of Pediatrics, National Research Center for Maternal and Child Health, University Medical Center, Nur-Sultan 010000, Kazakhstan

Corresponding author: Dimitri Poddighe, MD, MSc, PhD, Associate Professor, Director, Doctor, Pediatrics, National Research Center for Maternal and Child Health, No. 32 Turan Avenue, Nur-Sultan 010000, Kazakhstan. dimitri.poddighe@nu.edu.kz

Abstract

BACKGROUND

Even though coronavirus 2019 disease (COVID-19) clinical course in children is much milder than in adults, pneumonia can occur in the pediatric population as well. Here, we reported a single-center pediatric case series of COVID-19 from Kazakhstan during the first wave of pandemic.

AIM

To analyze the main clinical and laboratory aspects in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) positive and negative children diagnosed with pneumonia.

METHODS

This is a retrospective analysis of 54 children, who were medically assessed as close contacts of COVID-19 adults in their family setting, between June and September 2020. These children were all hospitalized: We compared the clinical and laboratory characteristics of children affected with pneumonia in the presence (group 1) or absence (group 2) of SARS-CoV-2 infection.

RESULTS

Overall, the main clinical manifestations at the admission were fever, cough, loss of appetite, fatigue/weakness, nasal congestion and/or rhinorrhea, and dyspnea. Based on the SARS-CoV-2 polymerase chain reaction (PCR) test, 24 positive children with pneumonia (group 1) and 20 negative children with pneumonia (group 2) were identified; 10 positive children did not show any radiological

findings of pneumonia. No significant differences were found between the two pneumonia study groups for any clinical and laboratory parameters, except for C-reactive protein (CRP). Of course, both pneumonia groups showed increased CRP values; however, the COVID-19 pneumonia group 1 showed a significantly higher increase of CRP compared to group 2.

CONCLUSION

In our case series of children assessed for SARS-CoV-2 infection based on contact tracing, the acute inflammatory response and, in detail, CRP increase resulted to be more pronounced in COVID-19 children with pneumonia than in children with SARS-CoV-2-unrelated pneumonia. However, because of multiple limitations of this study, larger, controlled and more complete clinical studies are needed to verify this finding.

Key Words: Pediatric COVID-19; SARS-CoV-2; Pneumonia; C-reactive protein; Chest X-ray; Inflammatory parameters

Core Tip: This is a single-center pediatric case series of coronavirus 2019 disease (COVID-19) from Kazakhstan during the first wave of pandemic. We analyzed the main clinical aspects in those children diagnosed with pneumonia. In detail, we compared the clinical and laboratory characteristics of children affected with pneumonia in the presence (group 1) or absence (group 2) of severe acute respiratory syndrome coronavirus-2 infection. No significant differences were found between these study groups for any clinical and laboratory parameters, except for C-reactive protein (CRP). Of course, both pneumonia groups showed increased CRP values, overall; however, COVID-19 pneumonia group showed a significantly higher increase of CRP compared to pneumonia children without COVID-19.

Citation: Zhamankulov A, Rozenson R, Morenko M, Akhmetova U, Tyo A, Poddighe D. Comparison between SARS-CoV-2 positive and negative pneumonia in children: A retrospective analysis at the beginning of the pandemic. *World J Exp Med* 2022; 12(2): 26-35

URL: https://www.wjgnet.com/2220-315x/full/v12/i2/26.htm

DOI: https://dx.doi.org/10.5493/wjem.v12.i2.26

INTRODUCTION

In December 2019, a new type of coronavirus infection rapidly spread from Wuhan city (in Hubei province, China), which was implicated in many cases of pneumonia and severe respiratory distress. On February 11th, 2020, the Research Group of the International Committee on Taxonomy of Viruses defined this new coronavirus as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and the World Health Organization (WHO) named the related infectious disease as coronavirus 2019 disease (COVID-19). On March 11th, 2020, the WHO announced a pandemic of COVID-19[1-3]. The Republic of Kazakhstan borders with China, and the first case of COVID-19 was registered on March 13th, 2020, in Almaty city. Accordingly, several restrictions were promptly implemented like in most parts of the world, which also affected the general medical practice and patients' management all over the country [4]. Overall, COVID-19 in children is characterized by a milder clinical course, in terms of both clinical manifestations and risk of complications[5]. According to the report from the American Academy of Pediatrics, as of September 17th, 2020 (thus, related to the first wave of pandemic), the proportion of pediatric COVID-19 diagnoses in the United States was only 10.3% of all the COVID-19 registered cases; the mortality rate in children was < 0.2%[6]. A study from China, including 2,143 pediatric patients, confirmed a mild clinical course of COVID-19 in most children and, indeed, only 5.9% of cases were diagnosed as severe in the same period[7]. Therefore, most pediatric COVID-19 cases showed an asymptomatic or mild clinical course[8-9]. The most commonly reported symptoms in children were fever and cough and, in general, respiratory manifestations (such as rhinorrhea, nasal congestion, undifferentiated upper airways inflammatory syndrome, dyspnea); however, gastrointestinal symptoms (including nausea, vomiting, abdominal pain, and diarrhea) were described as well[9-11]. Here, we reported a pediatric case series of COVID-19 from Kazakhstan. In detail, we analyzed the development of pneumonia in children medically and microbiologically assessed for SARS-CoV-2 infection in the context of a household contact tracing strategy implemented at the beginning of the pandemic.

MATERIALS AND METHODS

We retrospectively analyzed the medical records of 54 children aged 5 days to 17 years, who were medically assessed and hospitalized since they were close contacts of COVID-19 adult patients in their family setting. In detail, all these children were consecutively admitted and assessed at the Emergency Department of the multidisciplinary Children's Municipal Hospital No. 1 in Nur-Sultan (Kazakhstan), from June 8th to September 15th, 2020, because they were diagnosed with SARS-CoV-2 infection and/or affected with pneumonia. Indeed, this case series is a part of all those pediatric patients that received medical attention at the Emergency Department of Children's Municipal Hospital No. 1, because of previous close contact with a family member diagnosed with COVID-19, as already mentioned. All these children underwent SARS-CoV-2 polymerase chain reaction (PCR) test, but only those who resulted to be PCR positive and/or were diagnosed with pneumonia (even despite the negative PCR result), were admitted to the department of Pulmonology. Indeed, children who had contact with family members diagnosed with COVID-19 but resulted to be PCR negative and without pneumonia, were not admitted to the hospital and, thus, were discharged from the Emergency Department; unfortunately, these data could not be reliably retrieved. In order to assess the infection with SARS-CoV-2 in these children, the biospecimen was obtained by oropharyngeal swab, and the samples were placed in 3 mL of transport medium, in order to be delivered to the authorized laboratory according to the rules approved by the Ministry of Health of Republic of Kazakhstan (protocol No. 15990). The analysis of the viral RNA presence (by SARS-CoV-2 PCR test) was carried out by using the diagnostic kit KH-G-M-565-48-CE (manufactured by Shanghai Kehua Bio-engineering Co., Ltd; analyzer Xi'an Tian Long Science and Technology Co., Ltd., Shaanxi, China). Upon admission to the hospital, these children underwent a complete clinical examination (including an accurate collection of personal and family history) and first-level diagnostic work-up (including a complete blood cell count -CBC-, erythrocyte sedimentation rate -ESR-, urinalysis and general biochemistry). The biochemical analyses included plasmatic calcium, glucose, sodium, potassium, chloride, urea, creatinine, total protein, alanine aminotransferase, aspartate aminotransferase, bilirubin, creatine phosphokinase, in addition to serum C-reactive protein (CRP). All patients received a chest X-ray, in addition to the SARS-CoV-2 PCR test, as mentioned above. Additionally, according to the attending physician's recommendation for individual patients, the coagulation panel (including D-dimer) and additional laboratory tests (such as procalcitonin, lactate dehydrogenase, vitamin D) were performed in some patients only. Moreover, based upon the actual clinical condition and previous results, some children variably received a chest computerized tomography, abdominal ultrasound, renal ultrasound, echocardiography, electrocardiogram, cranial sonography (in patients younger than 1 year). Whenever these children received this additional diagnostic work-up, it was performed within the first week after the hospital admission. The clinical monitoring was established based on individual patients' condition. Temperature normalization, resolution of clinical symptoms, and 2 negative consecutive SARS-CoV-2 PCR tests were the adopted criteria to discharge these pediatric patients from the hospital. Data collection and descriptive analysis were carried out by Microsoft® Excel 2010 for Windows. Wherever appropriate and feasible, the statistical data analysis was performed: The differences in specific variables/parameters between two groups of patients were assessed for statistical significance by using the GraphPad Prism® software (version 4.0). In detail, laboratory parameters were expressed as mean ± SD error of the mean, because of the small and variable size of the study groups; accordingly, unpaired *t*-test (with Welch's correction) was used to compare two groups: P value < 0.05 was considered statistically significant.

RESULTS

Patients' demographic and study groups

Fifty-four children (age range: 5 days to 17 years; mean age and SD: 56 ± 55 mo) were assessed because of a positive SARS-CoV-2 PCR test and/or clinical/radiological finding of pneumonia after a close contact with a family member diagnosed with COVID-19. As graphically summarized in Figure 1, based on the SARS-CoV-2 PCR test and the radiological findings, 24 COVID-19 children with pneumonia (group 1) and 20 COVID-19 negative children with pneumonia (group 2) were identified, in addition to 10 SARS-CoV-2 PCR positive children who did not show any radiological findings of pneumonia. The detailed clinical and demographic characteristics of these 44 pneumonia children enrolled in the study are shown in Table 1. Overall, among all those 34 SARS-CoV-2 PCR positive children, 4 patients were completely asymptomatic (11.8%), 6 children were affected with upper airway acute respiratory infection (17.6%), and 24 patients developed mild to moderate pneumonia (70.6%). Among these 24 patients diagnosed with pneumonia (who represent our study population), the lung disease was bilateral in 17 cases, segmental in 5 cases, and subsegmental in 2 patients. Among those 20 SARS-CoV-2 PCR negative children diagnosed with lung disease, 15 children developed bilateral pneumonia and 5 patients showed unilateral subsegmental (always right-sided) pneumonia. All these radiological aspects are also summarized in Table 1.

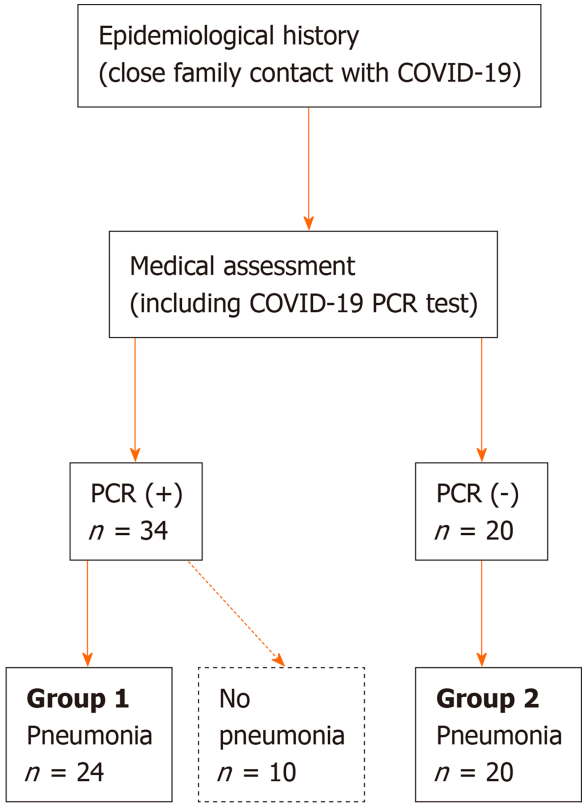
Table 1 Clinical and demographic characteristics of the study participants at the hospital admission

	Group 1 (PCR+ pneumonia)	Group 2 (PCR- pneumonia)
Patients		
Number	24	20
Gender		
Male	16 (66. 7%)	9 (45.0%)
Female	8 (33. 3%)	11(55.0%)
Age		
0-5 yr	14 (58. 3%)	11 (55.0%)
5-10 yr	4 (16. 7%)	4 (20.0%)
> 10 years	6 (25. 0%)	5 (25.0%)
Clinical manifestations		
Cough	17 (70. 8%)	15 (75.0%)
Fever	17 (70. 8%)	16 (80. 0%)
Dyspnea	7 (29. 2%)	7 (35. 0%)
Loss of appetite	15 (62. 5%)	13 (65.0%)
Fatigue	15 (62. 5%)	13 (65. 0%)
Weakness	15 (62. 5%)	13 (65. 0%)
Vomiting/nausea	2 (8. 3%)	3 (15. 0%)
Diarrhea	1 (4. 2%)	0 (0. 0%)
Flatulence	1 (4. 2%)	0 (0. 0%)
Rhinorrhea	8 (33. 3%)	9 (45. 0%)
Sweating	0 (0. 0%)	0 (0. 0%)
Chest pain	0 (0. 0%)	0 (0. 0%)
Dizziness	1 (4. 2%)	0 (0. 0%)
Joint pain	1 (4. 2%)	0 (0. 0%)
Seizures	0 (0. 0%)	0 (0. 0%)
Chest X ray findings		
Bilateral pneumonia	17 (70. 8%)	15 (75. 0%)
Segmental pneumonia	5 (20. 8%)	
Subsegmental pneumonia	2 (8. 3%)	5 (25.0%)
Comorbidity		
CHD	1 (4. 2%)	0 (0. 0%)
PTI	1 (4. 2%)	0 (0. 0%)
AML	1 (4. 2%)	0 (0. 0%)
Partial epilepsy	0 (0. 0%)	0 (0. 0%)

CHD: Congenital heart disease; PTI: Idiopathic Thrombocytopenic Purpura, AML: Acute Myeloid Leukemia.

Patients' clinical characteristics

Overall, the main clinical manifestations at the admission were fever, cough (which was reported to be dry and not productive in most cases), loss of appetite, fatigue and weakness, nasal congestion and/or rhinorrhea, dyspnea, as summarized in Table 1. Gastrointestinal symptoms, such as vomiting/nausea, diarrhea, and flatulence, were unusual in our patients, and were mostly reported in children younger than 3 years. Only one 16-year patient complained of intense sweating, chest pain and dizziness, but he



DOI: 10.5493/wjem.v12.i2.26

Figure 1 Flowchart describing the patients' study enrollment according to the severe acute respiratory syndrome coronavirus-2 polymerase chain reaction testing and chest X-ray results. COVID-19: Coronavirus disease 2019; PCR: Polymerase chain reaction.

was affected with congenital heart disease (pulmonary artery stenosis). The differential descriptive analysis of all clinical manifestations according to the group designation is reported in Table 1. Therefore, the main chief complaints were fever and cough, overall. No statistically significant differences were noticed between these two groups in terms of frequency and type of clinical manifestations. Cough (overall, reported in around 72% of all pneumonia patients) was present in 70.8% and 75% patients of the COVID-19 positive and negative groups, respectively. Fever (that was detected in > 75% of the study participants, overall) was reported in 70.8% and 80% patients of COVID-19 positive and negative groups, respectively. As regards other concerning respiratory symptoms, dyspnea was detected in both groups without any statistical differences and, respectively, in 29.2% and 35% of COVID-19 positive and negative groups.

Laboratory investigations

All the available laboratory results are summarized in Table 2. No statistically significant differences were found between the study groups for any laboratory parameters, except for CRP. In detail, there was a statistically significant difference between COVID-19 positive and negative patients, in terms of CRP values (group 1: 41.47 ± 11.23 mg/L, group 2: 15.10 ± 4.21 mg/L; $P = 0.0361$). However, no intergroup significant differences were detected as regards ESR. In terms of CBC, no significant differences were detected between these pneumonia groups in the main hematological parameters (hemoglobin, thrombocytes count and total white blood cells). However, in terms of differential cell blood count (as described in Table 2), both groups of children with pneumonia showed a relative lymphocyte reduction and, conversely, neutrophil increase. As already mentioned, no significant differences were found for all the other biochemical parameters; however, as explained, these data were not available for all study participants as regards many parameters, which may have affected the results of the statistical analysis, of course.

Other radiological investigations

Unfortunately, data on additional radiological investigations were available for a minority of patients, except for abdominal ultrasound, which was performed in 34 patients: It resulted abnormal with diffuse and reactive changes in the liver in only 4 COVID-19 patients (11.8%), who actually did not complain of any abdominal symptoms. No additional ultrasonographic alterations were reported. In detail, as regards the kidneys, no pathological changes were observed at all. Only 3 children (complaining of chest pain) underwent chest ultrasound: All showed signs of a small pleural effusion. In detail, among

Table 2 Laboratory parameters in the two study groups of children

Laboratory parameters	Group 1 (PCR + pneumonia) *n* = 24	Group 2 (PCR - pneumonia) *n* = 20
HGB (g/L)	120 ± 3.97	119 ± 3.4
MCV (fL)	85.2 ± 2.6	83.9 ± 1.59
PLT (10^9/L)	280 ± 19.4	338 ± 18.6
WBC (10^9/L)	10.3 ± 0.85	9.5 ± 0.77
Lymphocytes (%)	28.3 ± 2.91	32.9 ± 3.4
Lymphocytes (10^9/L)	2.7 ± 0.31	3.1 ± 0.35
Neutrophils (%)	64.3 ± 3.35	60.8 ± 3.8
Neutrophils (10^9/L)	7.3 ± 0.75	6.3 ± 0.69
Monocytes (%)	5 ± 0.47	6.1 ± 0.64
Monocytes (10^9/L)	0.5 ± 0.06	0.5 ± 0.06
ESR (mm/h)	19.1 ± 2.36	18.4 ± 1.88
CRP (mg/L)	41.5 ± 11.2	15.1 ± 4.21
Total bilirubin (μmol/L)	7.2 ± 0.67	9.07 ± 0.94
Total proteins (g/L)	66.5 ± 1.85	62.3 ± 1.56
Creatinine (μmol/L)	43 ± 2.84	41.6 ± 4.32
Urea (mmol/L)	3.24 ± 0.29	3.47 ± 0.41
Ca (mmol/L)	2.25 ± 0.04	2.24 ± 0.05
K (mmol/L)	4.53 ± 0.24	4.79 ± 0.21
Na (mmol/L)	137 ± 0.50	138 ± 0.71
Cl[1] (mmol/L)	102 ± 1.22	104 ± 1.18
Glucose[1] (mmol/L)	4.66 ± 0.18	5.54 ± 0.58
ALT[1] (U/L)	24.6 ± 8.24	24.4 ± 4.78
AST[1] (U/L)	29.6 ± 3.88	30.5 ± 5.42
CK[1] (U/L)	70.2 ± 18.7	64 ± 14.3
LDH[1] (U/L)	399 ± 120	323 ± 189
PCT[1] (ng/mL)	0.5 ± 0.11	0.3 ± 0.09
D dimer[1] (μg/mL)	1.4 ± 0.35	0.1 ± 0.02
25 OH vitD[1] (ng/mL)	27.3 ± 3.79	25.3 ± 2.67

[1]The information is not available for all patients.
HGB: Hemoglobin; WBC: White blood cells; MCV: Mean corpuscular volume; ESR: Erythrocyte sedimentation rate; PLT: Platelets; CRP: C reactive protein; Ca: Total Calcium.; K: Potassium; Na: Sodium; Cl: Chloride; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatinkinase; LDH: Lactate dehydrogenase; PCT: Procalcitonin.

these patients, 2 were diagnosed with COVID-19 and one was SARS-CoV-2 negative.

DISCUSSION

Currently, a few articles on COVID-19 from Central Asia can be retrieved in the medical literature: As regards the first wave of pandemic, those are mainly epidemiological studies describing the outbreak situation until June 2020[12-15]. Our study is a single-center pediatric case series describing the clinical, laboratory and radiological characteristics of SARS-CoV-2 positive and negative Kazakhstani children with pneumonia, who were identified based on contact tracing in the household setting. The clinical

manifestations of these COVID-19 children in our study were not qualitatively and quantitatively different from those emerging from previous and larger case series during the first phase of the pandemic[16-18]. Interestingly, > 60% of our patients were younger than 5 years; however, this distribution may be easily biased by the different parental awareness for infants and young children: Indeed, as explained, we assessed all consecutive pediatric contacts of COVID-19 adults, who were addressed for medical evaluation at the hospital. Respiratory symptoms were the most frequent clinical manifestations and were complicated with pneumonia in several patients. Among 54 pediatric contacts with family members affected with COVID-19, only 34 children resulted to be SARS-CoV-2 PCR positive, and 24 of them (70.6%) were concomitantly diagnosed with pneumonia. This diagnostic rate of pneumonia among COVID-19 children was quite high in our case series, compared to similar studies from different countries (see later), in which contact tracing strategy was the main method used for participants' recruitment, like in the present study. For instance, Alsharrah *et al*[19] described a retrospective and monocentric case series including 134 pediatric COVID-19 patients who mostly (84%) acquired the infection from household contacts: 67.9% and 32.1% of these children were reported as asymptomatic or affected with mild symptoms or pneumonia, respectively. In detail, only 12 COVID-19 patients (around 9%) showed "abnormal chest X-ray findings", which is clearly a much lower rate of COVID-19 pneumonia than in our experience presented in this study. Another study from Italy described children consulted in a specific COVID-19 Hub Centre coordinating the medical services, including children's admission to the pediatric COVID-19 department of a single referral hospital. In this study, 208 children were assessed as suspected cases based on fever and/or respiratory symptoms, in addition to the exposure COVID-19-infected relatives or cohabitants. Out of 144 children who were SARS-CoV-2 PCR tested, 104 turned out positive, but only 30 children were admitted to the hospital for variable medical reasons: In most cases, the hospitalization was mainly driven by relative indications, such as the young age (< 12 mo) or the presence of pre-existing comorbidities, or the persistence of fever, rather than respiratory complications; as regards pneumonia specifically, these authors mentioned only 1 case in a 15-year girl[20]. As regards the type of lung involvement, in our case series no significant differences were noticed in terms of chest X-ray findings, between SARS-CoV-2 positive and negative patients with pneumonia. However, CRP values resulted to be statistically different between these two groups. CRP is the most widely used parameter for assessing the acute systemic inflammatory response in children requiring medical attention at the pediatric emergency department[21]. Our results are in contrast with the study by Zhao *et al*[22], who compared COVID-19 children (n = 23, all inpatient) with others diagnosed with Influenza A (n = 69, inpatient; n = 69, outpatient): Indeed, these authors reported the opposite situation, since CRP values were significantly higher in the latter disease than in COVID-19. However, the COVID-19 and Influenza A study groups included all types of patients in terms of clinical severity (30.4% and 40.6% children developed pneumonia, respectively) and not only those affected with pneumonia, unlike our present study. The patients' age in this study was comparable to that of our cases series. Another study Li *et al*[23] made the same etiological comparison, but here all the enrolled children (COVID-19, n = 57; or Influenza A, n = 59) were affected with pneumonia: Again, CRP values resulted to be significantly lower in COVID-19 patients (3.7 mg/L *vs* 15.1 mg/L, P = 0.001). In this study, the average patients' age was 18.7 mo and, thus, they were quite younger than ours. However, significant increases of CRP values were described in pediatric patients affected with severe forms. Therefore, our observations on CRP values are in contrast with the previous data from those few comparable studies and the general findings from larger clinical studies conducted during the first wave of pandemic. We cannot provide any clear explanation for our different observations, but we could speculate that our patients may have arrived at the medical attention at a later stage than what may have happened in other countries for some organizational reasons (*e.g.* different health system procedures; more rapid contact tracing system; others), and/or because additional viruses (*e.g.* Influenza A) were concomitantly implicated. However, a number of study limitations might have definitely affected our results. Unfortunately, because of the limited resources for a complete diagnostic work-up in each patient at this hospital, the incomplete assessment of some laboratory parameters (including PCT, D-dimer and LDH) in all patients did not allow us to fully analyze the systemic inflammatory background in our case series, which may have provided further insights into our observations on the CRP values and radiological findings. In this regard, no computerized tomography imaging was immediately indicated at that time in children: Indeed, this is a retrospective cross-sectional study performed at the Emergency Department, and chest computerized tomography may have been requested later (and, thus, not recorded in the clinical database available to our research team) based on the individual medical indication. Indeed, no precise information about the therapy and, in detail, the use of antibiotics (such as macrolides, which were usually prescribed in this first phase of COVID-19 pandemic)[24] was available to us. Moreover, the small sample size and the absence of a control (SARS-CoV-2 negative) group without pneumonia have further hampered the data interpretation. Finally, the specific patients' recruitment by family contact tracing might have affected these results as well.

CONCLUSION

In conclusion, in addition to a relatively high prevalence of pneumonia among Kazakhstani COVID-19 children diagnosed after contact tracing during the first wave of pandemic, we observed a significant difference in CRP values between SARS-CoV-2 positive and negative children affected with pneumonia, which may deserve further verification and investigations with larger clinical studies, due to the several limitations of this retrospective case series.

ARTICLE HIGHLIGHTS

Research background

Even though coronavirus 2019 disease (COVID-19) clinical course in children is much milder than in adults, pneumonia can occur in the pediatric population as well.

Research motivation

To report a single-center pediatric case series of COVID-19 from Kazakhstan during the first wave of pandemic.

Research objectives

To analyze the main clinical and laboratory aspects in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive and negative children diagnosed with pneumonia.

Research methods

Retrospective analysis of 54 children, who were medically assessed because they were close contacts of COVID-19 adults in their family setting, between June and September 2020. The clinical and laboratory characteristics of children affected with pneumonia in the presence (group 1) or absence (group 2) of SARS-CoV-2 infection, were compared.

Research results

No significant differences were found between the study groups for any clinical and laboratory parameters, except for C-reactive protein. Both pneumonia groups showed higher C-reactive protein values than COVID-19 children without pneumonia, overall; however, the COVID-19 pneumonia group 1 showed a significantly higher increase of C-reactive protein compared to group 2 (SARS-CoV-2 negative pneumonia).

Research conclusions

In our case series of children assessed for SARS-CoV-2 infection based on contact tracing, the acute inflammatory response and, in detail, C-reactive protein increase resulted to be more pronounced in COVID-19 children with pneumonia than in children with SARS-CoV-2 negative pneumonia.

Research perspectives

Larger, controlled and more complete clinical studies are needed to verify the different aspects of (acute) systemic inflammation in children with SARS-CoV-2 pneumonia.

FOOTNOTES

Author contributions: Zhamankulov A and Rozenson R conceived the study; Zhamankulov A, Morenko M, Akhmetova U, Tyo A collected and provided the data; Zhamankulov A and Poddighe D organized and analyzed the data; Rozenson R, Morenko M, Poddighe D provided intellectual contribution; Zhamankulov A and Poddighe D wrote the manuscript; all authors have read and agreed to the published version of the manuscript.

Institutional review board statement: Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by local Ethics Committee [protocol No. 2020.3.7 approved by Local Bioethical Committee of NJSC (Astana Medical University)] in agreement with the ethical principles of the State Standard for Good Clinical Practice and Regulatory Law of the Republic of Kazakhstan "On Science", State Educational Standard of the Republic of Kazakhstan 5.01.024-2008 "Scientific Research").

Informed consent statement: Informed consent was obtained from guardians of all patients involved in the study.

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

Data sharing statement: Dataset can be available upon request.

Country/Territory of origin: Kazakhstan

ORCID number: Adil Zhamankulov 0000-0002-9928-0617; Rafail Rozenson 0000-0001-6088-2269; Marina Morenko 0000-0001-9553-3560; Ulzhan Akhmetova 0000-0003-1656-5578; Alina Tyo 0000-0002-1467-6699; Dimitri Poddighe 0000-0001-6431-9334.

S-Editor: Xing YX
L-Editor: A
P-Editor: Xing YX

REFERENCES

1 **Zhu N**, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]
2 **She J**, Liu L, Liu W. COVID-19 epidemic: Disease characteristics in children. *J Med Virol* 2020; **92**: 747-754 [PMID: 32232980 DOI: 10.1002/jmv.25807]
3 **Cucinotta D**, Vanelli M. WHO Declares COVID-19 a Pandemic. *Acta Biomed* 2020; **91**: 157-160 [PMID: 32191675 DOI: 10.23750/abm.v91i1.9397]
4 **Mukusheva Z**, Assylbekova M, Poddighe D. Management of pediatric rheumatic patients in Kazakhstan during the coronavirus disease 2019 (COVID-19) pandemic. *Rheumatol Int* 2020; **40**: 1351-1352 [PMID: 32514608 DOI: 10.1007/s00296-020-04613-5]
5 **Rabi FA**, Al Zoubi MS, Al-Iede MM, Kasasbeh G, Badran EF. Coronaviruses in children: A review of potential mechanisms of childhood protection. *Acta Paediatr* 2021; **110**: 765-772 [PMID: 33247469 DOI: 10.1111/apa.15691]
6 **American Academy of Pediatrics and Children's Hospital Association**. Children and COVID-19: State Data Report. Available from: https://downloads.aap.org/AAP/PDF/AAP%20and%20CHA%20-%20Children%20and%20COVID-19%20State%20Data%20Report%207.30.20%20FINAL.pdf
7 **Dong Y**, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, Tong S. Epidemiology of COVID-19 Among Children in China. *Pediatrics* 2020; **145** [PMID: 32179660 DOI: 10.1542/peds.2020-0702]
8 **Tiruneh FT**. Clinical Profile of Covid-19 in Children, Review of Existing Literatures. *Pediatric Health Med Ther* 2020; **11**: 385-392 [PMID: 33061744 DOI: 10.2147/PHMT.S266063]
9 **de Souza TH**, Nadal JA, Nogueira RJN, Pereira RM, Brandão MB. Clinical manifestations of children with COVID-19: A systematic review. *Pediatr Pulmonol* 2020; **55**: 1892-1899 [PMID: 32492251 DOI: 10.1002/ppul.24885]
10 **Zimmermann P**, Curtis N. COVID-19 in Children, Pregnancy and Neonates: A Review of Epidemiologic and Clinical Features. *Pediatr Infect Dis J* 2020; **39**: 469-477 [PMID: 32398569 DOI: 10.1097/INF.0000000000002700]
11 **Yasuhara J**, Kuno T, Takagi H, Sumitomo N. Clinical characteristics of COVID-19 in children: A systematic review. *Pediatr Pulmonol* 2020; **55**: 2565-2575 [PMID: 32725955 DOI: 10.1002/ppul.24991]
12 **Maukayeva S**, Karimova S. Epidemiologic character of COVID-19 in Kazakhstan: A preliminary report. *North Clin Istanb* 2020; **7**: 210-213 [PMID: 32478290 DOI: 10.14744/nci.2020.62443]
13 **Semenova Y**, Glushkova N, Pivina L, Khismetova Z, Zhunussov Y, Sandybaev M, Ivankov A. Epidemiological Characteristics and Forecast of COVID-19 Outbreak in the Republic of Kazakhstan. *J Korean Med Sci* 2020; **35**: e227 [PMID: 32567261 DOI: 10.3346/jkms.2020.35.e227]
14 **Kim K**, Choi JW, Moon J, Akilov H, Tuychiev L, Rakhimov B, Min KS. Clinical Features of COVID-19 in Uzbekistan. *J Korean Med Sci* 2020; **35**: e404 [PMID: 33230989 DOI: 10.3346/jkms.2020.35.e404]
15 **Bayesheva D**, Boranbayeva R, Turdalina B, Fakhradiyev I, Saliev T, Tanabayeva S, Zhussupov B, Nurgozhin T. COVID-19 in the paediatric population of Kazakhstan. *Paediatr Int Child Health* 2021; **47**: 76-82 [DOI: 10.1080/20469047.2020.1857101]
16 **Ludvigsson JF**. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr* 2020; **109**: 1088-1095 [PMID: 32202343 DOI: 10.1111/apa.15270]
17 **Hoang A**, Chorath K, Moreira A, Evans M, Burmeister-Morton F, Burmeister F, Naqvi R, Petershack M. COVID-19 in 7780 pediatric patients: A systematic review. *EClinicalMedicine* 2020; **24**: 100433 [PMID: 32766542 DOI: 10.1016/j.eclinm.2020.100433]
18 **Chang TH**, Wu JL, Chang LY. Clinical characteristics and diagnostic challenges of pediatric COVID-19: A systematic review and meta-analysis. *J Formos Med Assoc* 2020; **119**: 982-989 [PMID: 32307322 DOI: 10.1016/j.jfma.2020.04.007]
19 **Alsharrah D**, Alhaddad F, Alyaseen M, Aljamaan S, Almutairi N, Ayed M, Papenburg J, Alghounaim M. Clinical characteristics of pediatric SARS-CoV-2 infection and coronavirus disease 2019 (COVID-19) in Kuwait. *J Med Virol* 2021; **93**: 3246-3250 [PMID: 33219559 DOI: 10.1002/jmv.26684]
20 **Nunziata F**, Bruzzese E, Poeta M, Pierri L, Catzola A, Ciccarelli GP, Vassallo E, Montella E, Lo Vecchio A, Guarino A. Health-care organization for the management and surveillance of SARS-CoV-2 infection in children during pandemic in

Campania region, Italy. *Ital J Pediatr* 2020; **46**: 170 [PMID: 33198780 DOI: 10.1186/s13052-020-00928-y]

21 **Poddighe D**. Common finding of mild hyponatremia in children evaluated at the Emergency Department and its correlation with plasma C-reactive protein values. *Minerva Pediatr* 2016; **68**: 173-176 [PMID: 27125438]

22 **Zhao Y**, Sun L, Bouchard HC, Zhang XX, Wan G, Hao YW, He SX, Jiang YY, Pang L. Coronavirus Disease 2019 *versus* Influenza A in Children: An Observational Control Study in China. *Biomed Environ Sci* 2020; **33**: 614-619 [PMID: 32933613 DOI: 10.3967/bes2020.080]

23 **Li Y**, Wang H, Wang F, Du H, Liu X, Chen P, Wang Y, Lu X. Comparison of hospitalized patients with pneumonia caused by COVID-19 and influenza A in children under 5 years. *Int J Infect Dis* 2020; **98**: 80-83 [PMID: 32535301 DOI: 10.1016/j.ijid.2020.06.026]

24 **Poddighe D**, Aljofan M. Clinical evidences on the antiviral properties of macrolide antibiotics in the COVID-19 era and beyond. *Antivir Chem Chemother* 2020; **28**: 2040206620961712 [PMID: 32972196 DOI: 10.1177/2040206620961712]

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