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Contents

Quarterly Volume 12 Number 3 September 18, 2024

EDITORIAL

REVIEW

MINIREVIEWS

SYSTEMATIC REVIEWS

META-ANALYSIS

World Journal of Meta-Analysis

Quarterly Volume 12 Number 3 September 18, 2024

Contents

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EDITORIAL

Role of long non-coding RNAs in non-alcoholic fatty liver disease

Anju Mullath, Murali Krishna

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is emerging as a common cause of chronic liver disease in children and adults. NAFLD can progress to steatohepatitis and potentially even hepatocellular carcinoma. Early identification of patients at risk for progressive disease is crucial for managing NAFLD. Recent studies have identified long noncoding RNAs (lncRNAs), circular RNAs, and microRNAs as playing important roles in the pathogenesis of NAFLD. These noncoding RNAs are involved in modulating several metabolic pathways such as hepatic glucose and lipid metabolism, oxidative stress, and even carcinogenesis. Elevated levels of lncARSR and lncRNA nuclear-enriched abundant transcript 1 have been found in patients with NAFLD. In addition, lncRNAs such as PRYP4-3 and RP11-128N14.5 can distinguish patients with NAFLD from healthy indi-viduals. Increased MEG3 expression has been observed in both NAFLD and non-alcoholic steatohepatitis, suggesting that it may help predict patients at risk for disease progression. With advances in transcriptomics, we may discover additional targets to help in the identification and prognostication of NAFLD.

Key Words: Long noncoding RNA; Non-alcoholic fatty liver disease; Plasmacytoma variant translocation 1; Nuclear-enriched abundant transcript 1; Muscle- and adipose-associated long intergenic non-coding RNA; H19

Core Tip: Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver ailments. Early diagnosis and treatment can help mitigate its impact on the liver. The role of long non-coding RNAs (lncRNAs) in the pathogenesis of NAFLD has been the subject of research for some time. LncRNAs such as plasmacytoma variant translocation 1, nuclear-enriched abundant transcript 1, muscle- and adipose-associated long intergenic non-coding RNA, and H19 have been shown to play important roles in the disease process of NAFLD.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has emerged as one of the most prevalent causes of chronic liver disease globally. However, a lack of awareness surrounding this seemingly benign condition exacerbates the issue. NAFLD frequently manifests as part of metabolic syndrome, which includes obesity and type 2 diabetes[1]. The spectrum of NAFLD encompasses non-alcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma.

Long non-coding RNAs (lncRNAs) are transcripts exceeding 200 nucleotides and are intricately involved in various functions such as post-transcriptional regulation and epigenetic modifications. Recent research has uncovered the role lncRNAs play in several disease processes. These molecules hold promise as agents for diagnosis and prognostication in the near future.

ROLE OF LNCRNA IN NAFLD

Among non-coding RNAs, lncRNAs are believed to play a crucial role in regulating hepatic gluconeogenesis, inflammation, hepatic regeneration, and fibrosis. Several candidates have been identified thus far, including plasmacytoma variant translocation 1 (PVT1), nuclear-enriched abundant transcript 1 (NEAT1), PRYP4.3, RP 11-128N14.5, HCG18, and MEG3[2]. In this editorial, we will delve into four promising markers that may potentially revolutionize the diagnosis and management of NAFLD in the future.

PVT1

LncRNA PVT1 has garnered significant attention in the context of NAFLD owing to its multifaceted roles in hepatic pathophysiology. Studies have elucidated its involvement in diverse biological processes, including hepatic lipid metabolism, inflammation, and fibrosis, all of which are central to the progression of NAFLD. The dysregulation of PVT1 has been implicated in exacerbating liver injury and fibrosis severity in patients with NAFLD[3]. Moreover, elevated PVT1 expression levels have been correlated with the presence of steatosis and the degree of liver inflammation in NAFLD cohorts[4]. PVT1 affects liver fat metabolism by reducing the levels of microRNA (miR)-20a-5p. Mir-20a-5p acts by suppressing the expression of CD36, which, in turn, reduces lipid accumulation by binding to the 3′-untranslated region[5]. CD36 plays a crucial role in regulating inflammation, fatty acid oxidation, and intracellular fatty acid homeostasis.

Emerging evidence suggests that PVT1 holds promise as a diagnostic and prognostic biomarker for NAFLD. Its overexpression in hepatic tissues and circulation has been proposed as a potential indicator of the onset and progression of NAFLD[6]. Additionally, aberrant expression of PVT1 has been associated with adverse clinical outcomes, including liver cirrhosis and hepatocellular carcinoma, further underscoring its significance in the pathogenesis of NAFLD[7].

Targeting PVT1 presents a novel therapeutic avenue for managing NAFLD. Inhibition of PVT1 expression has shown promise in ameliorating hepatic steatosis, inflammation, and fibrosis in preclinical models, suggesting its potential as a therapeutic target for NAFLD intervention[8].

NEAT1

LncRNA NEAT1 has emerged as a pivotal player in the pathogenesis of NAFLD. Dysregulation of NEAT1 has been implicated in various aspects of the progression of NAFLD, including hepatic lipid metabolism, inflammation, and fibrosis[9]. Studies have revealed elevated NEAT1 expression levels in the liver tissues and circulation of patients with NAFLD, suggesting its potential as a diagnostic biomarker for the disease[10].

Table 1 Various long non-coding RNAs implicated in non-alcoholic fatty liver disease

Gene	Principal functions	Upregulated/downregulated
Gm9795	Endoplasmic reticulum stress Promoting inflammatory response	Upregulated
Platr4	Promoting inflammatory response	Upregulated
HOTAIR	Promoting lipid accumulation	Upregulated
LncTNF	Promoting inflammation	Upregulated
Gm15622	Promoting lipid accumulation	Upregulated
LncHR1	Preventing the accumulation of fatty acids and triglyceride	Downregulated
SRD5A3-AS1	Promoting cell proliferation, steatosis, inflammation and fibrosis	Downregulated
Gm16551	Promoting de novo lipogenesis	Downregulated
AC012668	Promoting lipid accumulation	Downregulated
Mirt2	Promoting hepatic steatosis	Downregulated

NEAT1 exerts its effects through diverse mechanisms, including the regulation of gene expression, chromatin organization, and nuclear structure maintenance[11]. In NAFLD, NEAT1 has been shown to modulate key signaling pathways involved in lipid accumulation, hepatic steatosis, and inflammation, thereby contributing to the pathogenesis of the disease[12]. NEAT1 Levels were found to be increased in patients with NAFLD, and higher NEAT1 Levels correlated with reduced levels of miR-212-5p. This miRNA is known to inhibit the activity of fatty acid synthase, and its inhibition has been shown to result in triglyceride accumulation in mouse primary hepatocytes[13].

Furthermore, NEAT1 has been implicated in promoting hepatic fibrosis through its interaction with various proteins and miRNAs, highlighting its multifaceted role in the progression of NAFLD[14]. Given its intricate involvement in the pathophysiology of NAFLD, NEAT1 represents a promising therapeutic target for developing novel interventions aimed at mitigating disease progression and improving clinical outcomes.

MUSCLE- AND ADIPOSE-ASSOCIATED LONG INTERGENIC NON-CODING RNA (MAYA)

LncRNA MAYA has emerged as a novel regulator of metabolic disorders, including NAFLD. The expression of MAYA is dysregulated in patients with NAFLD, suggesting its potential role in disease pathogenesis[15]. Recent studies have implicated MAYA in modulating lipid metabolism, insulin sensitivity, and inflammation in hepatic tissues, thereby contributing to the development and progression and NAFLD[15]. MAYA regulates the Hippo signaling pathway, which, when activated, leads to the repression of downstream transcriptional co-activators YAP and TAZ. The Hippo signaling pathway also plays a role in liver fibrosis.

Additionally, MAYA has been proposed as a diagnostic biomarker for NAFLD owing to its differential expression patterns in liver tissues and circulation of patients with NAFLD compared to healthy controls[16]. Further elucidation of the molecular mechanisms and functional significance of MAYA may unveil novel therapeutic targets for NAFLD intervention.

H19

LncRNA H19 has garnered considerable attention in the realm of NAFLD owing to its regulatory roles in hepatic lipid metabolism and inflammation. H19 expression levels are dysregulated in patients with NAFLD, suggesting its involvement in disease pathogenesis[17]. Mechanistically, H19 has been implicated in modulating key signaling pathways related to lipid accumulation, hepatic steatosis, and inflammation in the liver[18]. H19 downregulates the expression of miR-130a, which further inhibits the expression of PPARγ, and promotes steatosis by upregulating the transcription factor MLXIPL (also known as ChREBP)[17]. Furthermore, aberrant H19 expression has been correlated with the severity of liver injury and fibrosis in NAFLD cohorts[19]. Given its potential as a diagnostic and prognostic biomarker, further investigation into the functional significance of H19 in the pathophysiology of NAFLD may unveil novel therapeutic targets for disease intervention.

Table 1 provides a brief overview of other lncRNAs that are upregulated or downregulated in NAFLD[2].

CONCLUSION

NAFLD is emerging as the leading liver ailment with far-reaching effects on patient morbidity and mortality. Early

markers for diagnosis and prognostication will help in design and implementation of appropriate steps to ameliorate the condition. LncRNAs can play an important role in both these aspects, and further research is required to improve our understanding of their functions and potential applications.

FOOTNOTES

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REVIEW

Mechanisms of vascular injury in neurotrauma: A critical review of the literature

Jonathan Willman, Annu Lisa Kurian, Brandon Lucke-Wold

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Abstract

One in every two individuals will experience a traumatic brain injury in their lifetime with significant impacts on the global economy and healthcare system each year. Neurovascular injury is a key aspect of neurotrauma to both the brain and the spinal cord and an important avenue of current and future research seeking innovative therapies. In this paper, we discuss primary and secondary neurotrauma, mechanisms of injury, the glymphatic system, repair and recovery. Each of these topics are directly connected to the vasculature of the central nervous system, affecting severity of injury and recovery. Consequently, neurovascular injury in trauma represents a promising target for future therapeutics and innovation.

Key Words: Neurotrauma; Neurovascular injury; Primary neurotrauma; Secondary neurotrauma; Traumatic brain injury; Traumatic spinal cord injury; Glymphatic system; Vascular Injury

Core Tip: Primary neurotrauma is an initial mechanical insult to the central nervous system. Secondary neurotrauma involves metabolic and cellular derangements that occur days to months after the initial insult. Together, this neurotrauma disrupts cerebral autoregulation and neurovascular coupling, leading to derangements in neurovascular flow and blood-brain barrier dysfunction. Similarly, the glymphatic system, responsible for clearing waste products through the perivascular space, becomes impaired following neurotrauma, leading to increased protein deposition and cognitive decline. Emerging therapeutics focus on reducing neuroedema, decreasing blood-brain barrier dysfunction, and promoting neuroregeneration.

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INTRODUCTION

Statistics suggest that one in every two individuals will experience a traumatic brain injury (TBI) in their lifetimes and the ensuing cost to the global economy has grown upwards of 400 billion United States dollars per year[1]. As a result, TBI remains a grave social, economic, and clinical concern.

Disruption and damage to the vascular unit and perivascular glymphatic system may play integral roles in the mechanisms underlying neurotrauma in the immediate and long-term setting[2]. It follows that the vascular disturbances associated with neurotrauma represent a significant avenue of prognostication and treatment for the future of neurotrauma therapy in both TBI and traumatic spinal cord injuries (TSCI).

TBIs may occur in any demographic and range in intensity from severe to moderate to mild. However, the majority of TBI cases are mild and, amongst adult patients, most are male[3]. This sex difference is commonly attributed to an association between male sex and increased 'risk-taking behavior'[4]. Similarly, TSCI most often occur in males and the elderly with less than one-third of cases resulting from motor vehicle collisions, less than one-third from occupation accidents, and the remainder from other causes[5-7]. The majority of TSCIs are cervical injuries which have the highest mortality rates when compared with thoracic or lumbar lesions[6]. In addition, TSCIs are associated with significant morbidity and medical costs, even years after the primary hospital stay with pressure ulcers and urological concerns being some of the most common causes of readmission[8]. Likewise, even mild TBI patients may report long-lasting symptoms. A subgroup of mild TBI patients report persistent symptoms of reduced cognitive ability and depressed mood months to years after the initial TBI[9-11]. The elderly and those with reduced cognitive reserve appear to be at highest risk for persistent symptoms[10,12]. Common chronic ailments associated with TBI include but are not limited to sleep disturbances, cognitive deficits, depression, post-traumatic stress disorder (PTSD), chronic pain, and increased risk of neurodegenerative diseases[13]. Studies of blast-related TBIs in soldiers appear to exhibit even higher rates of comorbidities such as headache, PTSD, and anxiety[14]. While recent advances in helmet design have reduced the number and severity of TBIs, there has been little reduction in the occurrence of SCIs[15]. Consequently, although admittedly less common, SCIs in the primary occurrence setting remain a largely unaddressed cause of morbidity and mortality. With the growing elderly population worldwide and corresponding higher rates, SCI burden is predicted to increase globally in the coming years[16].

PRIMARY NEUROTRAUMA

Neurotrauma is divided into two stages: Primary trauma and secondary trauma. Primary trauma is defined by the initial neurological and vascular insult caused by direct mechanical forces acting on the central nervous system (CNS)[17]. The mechanism of trauma may vary from blunt to penetrating and may include projectile, nonprojectile, or blast-associated [17,18]. Neurotrauma may result in a number of immediate gross vascular consequences including epidural hematoma, subdural hematoma, subarachnoid hemorrhage, and intraparenchymal bleeds, in addition to neuronal lesions such as diffuse axonal injury (DAI)[17]. However, not all primary vascular injury is macroscopic. There is growing evidence that primary neurotrauma may cause significant microvascular injury which may lead directly to substantial secondary trauma[18]. A recent study by Reiter *et al*[19] examined how mechanical impacts displaced human and porcine neurons and vessels in brain tissue. They found that neurons surrounding blood vessels displaced further creating a heterogeneous interface between two entities, potentially generating an environment of substantial strain on the vessels[19]. Blast injuries, in particular, stress the microvessels and damage the endothelium and surrounding micro environment[2].

Cortical spreading depolarization (CSD) is a term that refers to electrical derangement, depolarization, neuronal swelling, and vascular constriction following a CNS insult such as neurotrauma[20]. This vasoconstriction in the setting of TBI may significantly exacerbate ischemia and contribute to morbidity[21]. As it has been estimated that over one-half of patients with TBI experience this sequence of events, CSD represents another significant avenue of future research in the field of neurotrauma vascular pathogenesis[20].

Primary neurotrauma may be further subdivided into primary TBI and primary SCI.

Primary neurotrauma-mechanisms of traumatic brain injury

Based on the pattern of injury TBI may be further subdivided into focal and diffuse injuries[22]. Focal injuries are predominantly due to the linear acceleration of an impact[23]. The skull may warp or fracture on the "coup" side (the same side as the impact) causing vascular trauma with associated contusions or meningeal arterial trauma with an associated epidural hematoma[22-25]. On the opposite side of the brain from the linear impact, a "contrecoup" injury may occur due to the rebound of the brain within the skull[24]. These injuries may cause damage to the bridging cortical veins with a resultant subdural hematoma[24].

Diffuse injuries, on the other hand, are more strongly associated with rotational or angular acceleration[23]. This type of acceleration is often caused by oblique impacts and may cause significant white matter and microvascular deformation [26]. The growing body of evidence suggests that, while previously overlooked, rotational acceleration may cause as much or more trauma as linear acceleration[26,27]. Specifically, rotational acceleration may cause both diffuse vascular injury and DAI through sheering forces[25,28-31]. This DAI is characterized by extensive microtubule and axonal trauma with resultant synapse failure and apoptosis[32-34]. This DAI results in extensive real-world consequences both economically and in patient outcomes with chronic neurological deficits[34]. One study by Lota *et al*[35] examined impacts in combat sports and found high rates of rotational acceleration in mixed martial arts, boxing, and taekwondo, yet headgear use alone, much less headgear designed to mitigate rotational acceleration, remains contentious.

The field of TBI therapy research is quickly changing. For example, Mesenchymal stem cell-derived extracellular vesicles is one promising treatment that, in the lab setting, appears to stabilize vascular trauma, reduce inflammation, and promote neuroprotection[36,37]. However, further research is needed to clarify real-world benefits and ideal routes of delivery. Virtual reality-based therapy represents another novel treatment that may represent a useful tool for alleviating cognitive and mood dysfunctions post-TBI[38,39]. In short, there are numerous studies examining disparate routes of treatment for TBI.

Primary neurotrauma-mechanisms of traumatic spinal cord injury

TSCI may cause autonomic dysfunction, motor inhibition with damage to the corticospinal tract, and loss of sensation with damage to the spinothalamic tract or gracillis-cuneatus fasciculi of the dorsal columns[40-42]. In addition, TSCI may include damage or pressure on structures surrounding the cord, including ligaments, vertebrae, and vessels[40]. Particularly vulnerable vessels include the single anterior spinal artery and the duo of posterior spinal arteries[40]. Radicular arteries also play a vital role with the artery of Adamkiewicz contributing to the vascular supply of the lower segments of the spinal cord[40,41].

There are four primary mechanisms of force delivery to the spine[43]. These include axial compression, flexion compression, distraction, and rotational force[43]. Axial or vertical compression is commonly associated with burst fractures, especially of the thoracolumbar region[43-45]. Similarly, flexion compression is often associated with compression fractures of the anterior spinal column and a distinct "wedge fracture" [43,46,47]. Distraction force, which is essentially stretching force acting on the spine, has been associated with significant rates of blunt vascular trauma especially in the cervical region[48,49]. This force must often be significant to overpower spinal ligaments[50]. Rotational force especially when combined with other forces may result in significant damage to the cord and may cause vascular dissection, especially in the cervical region[43,51].

Furthermore, there are four main categories of TSCI[52]. These include TSCI with transient compression of the cord in which the initial cause of the compression is acutely self-corrected, TSCI with persistent compression of the cord in which the lesion remains uncorrected, distraction injury in which the spine remains extended due to a persistent lesion, and lastly direct laceration or transection in which the neural and vascular pathways are transected[52]. Compression, distraction, and laceration may all cause axonal and vascular disruption with ischemia and significant sequela[53].

In the setting of acute TSCI and traumatic stenosis, urgent surgery must often be performed with the goal decompressing vascular and neuronal lesions and stabilizing the spine[54] (Figure 1).

SECONDARY NEUROTRAUMA

The immediate effects of primary neurotrauma are followed by secondary neurotrauma which is a collection of metabolic and cellular derangements that occur for days to months after the initial force event[17]. This cascade includes ischemia, excitotoxicity, oxidative stress, mitochondrial and endoplasmic reticulum dysfunction, vasogenic and cytotoxic edema, immune cell derangement, and neuronal cell death[17,55-58]. Excitotoxicity refers to the early release and failure of clearance of high concentrations of excitatory neurotransmitters such as glutamate and the consequent spreading depolarization or activation that occurs as a result[56]. Excitotoxicity is a neuronal derangement that has been identified in many CNS ailments from ischemic strokes to Alzheimer's disease[59].

The cell lysis from primary neurotrauma causes an increase in extracellular glutamate which binds N-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors receptors which causes an influx of both calcium and sodium ions[60,61]. This influx of ions leads to deleterious effects on both the endoplasmic reticulum and the mitochondria[60]. Under normal conditions, mitochondria contain a complex and delicate network of membranes and channels that allow for oxidation and reduction through the electron transport chain[62,63]. The increased levels of intracellular calcium activate enzymes that damage the mitochondrial membrane, which in turn increases intra-organelle calcium levels, uncouples the mitochondrial electron transport chain, releases free radicals including reactive oxygen

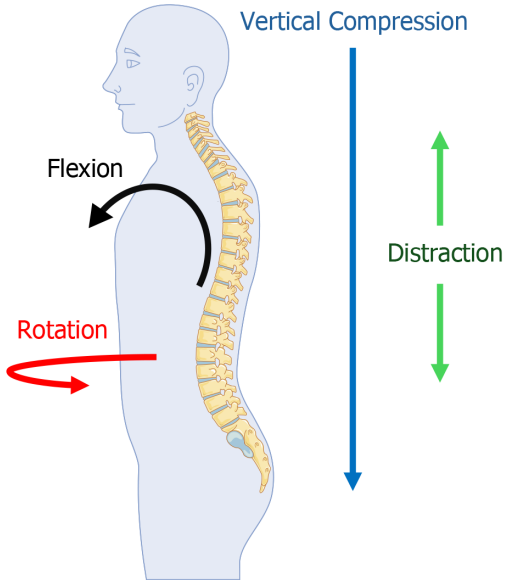

Figure 1 In the setting of traumatic spinal cord injuries, forces can act on the spine in a number of fashions with unique consequences. Some of those force directionalities include vertical compression, distraction, rotation, and flexion. Parts of the figure were drawn by using modified pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

species, and triggers the activation of pro-apoptotic factors, and ultimately cell death[56,64,65]. As free radical formation and ischemia increase due to neurotrauma, there is a resultant increase in misfolded proteins within the endoplasmic reticulum (ER), a major site of protein production[57,66,67]. This causes an activation of the unfolded protein response (UPR)[68]. Persistent ER stress, free radical formation, and failed resolution of elevated protein misfolding cause the three sensor elements of the UPR, inositol-requiring protein 1 (IRE1), protein kinase RNA-like ER kinase (PERK), and activating transcription factor-6 (ATF6) to dissociate from the stabilizing protein GRP78[68]. IRE1 ultimately activates apoptotic protease-activating factor 1 (Apaf1)-dependent caspase, while PERK and ATF6 induce the pro-apoptotic factor C/EBP homologous protein[68]. Together, these proteins induce cell death[68].

Immune cell derangement is common post-neurotrauma. Levels of neutrophils in particular are elevated within CNS tissue immediately post neurotrauma, possibly as a result of elevated catecholamine concentrations[69]. These neutrophils play a significant role in ROS and inflammatory generation in the first days of recovery[69]. There is even some evidence that immune cells may contribute to blood-brain barrier (BBB) breakdown within minutes of an impact[55,69].

There are two forms of edema that occur as a consequence of neurotrauma: vasogenic and cytotoxic edema. Vasogenic edema is the expansion of extracellular fluid as a result of CNS vascular injury[58]. Conversely, cytotoxic edema is intracellular edema caused by the pathologic accumulation of ions such as sodium within cells, post neurotrauma[58].

GLYMPHATIC SYSTEM

While it had long been believed that cerebral spinal fluid (CSF) ultimately drained into the lymphatic system, it was not until 2012 with the publication of a seminal paper by Iliff, Nedergaard, and colleagues that the CNS connection to the lymphatic system was discovered[70-72]. In their paper, Iliff *et al*[72] coined the term "glymphatic" by combining glial and lymphatic. This discovery has had substantial effects on the field since.

The glymphatic system is a perivascular network of astrocyte foot processes that create a space beneath the BBB where CSF and interstitial fluid between neuronal cells may cycle[70,73]. This is chiefly accomplished through aquaporin 4 (AQP4) water channels and allows for the clearance of waste products from neuronal tissue[73]. Ultimately, the CSF is absorbed by the arachnoid granulations or cervical lymphatics and is thus cleared from the CNS[70]. Following neurotrauma, the AQP4 channels become depolarized, and glymphatic system clearance becomes greatly impaired[74,75]. This appears to cause an increase in detrimental protein deposition including tau and amyloid beta and may account for some of the cognitive depression following TBI[74]. In addition, as the glymphatic system is naturally most active during sleep, there is some evidence that sleep disturbances caused by neurotrauma may contribute to a negative cycle of reduced sleep quality and worsening glymphatic function[70,76].

Consequently, the theoretical benefits of future therapeutics that might target glymphatic system malfunction in neurotrauma could include enhanced clearance of toxic excitatory or inflammatory byproducts and improved recovery (Figure 2).

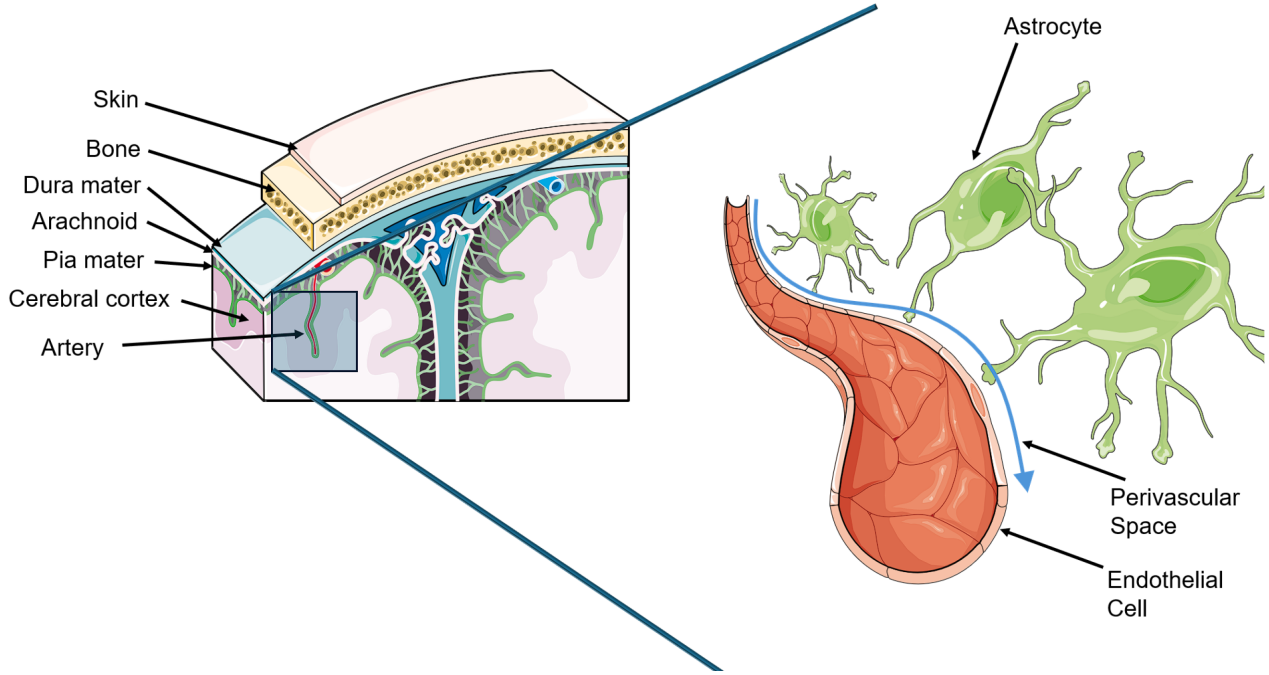

Figure 2 The perivascular space created by the interplay between the central nervous system blood vessels and the foot processes of the astrocytes allows for the cycling of waste through the cerebral spinal fluid and interstitial fluids. Parts of the figure were drawn by using modified pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

EFFECTS OF NEUROTRAUMA ON THE NEUROVASCULATURE

Cerebrovascular disruption in CNS injuries can have significant effects due to impairment of cerebral autoregulation, a key factor influencing cerebral perfusion pressure, even when vascular injury is not apparent.

The CNS relies heavily on a consistent blood supply that dynamically adjusts to its metabolic demands through neurovascular units (NVUs)[77]. NVUs consist of endothelial cells, smooth muscle cells, pericytes, neurons, and perivascular astrocytes, working together to regulate cerebral blood flow, vascular permeability, and nutrient supply[77]. The endothelial cells form part of the BBB, which tightly controls the exchange of substances between the systemic circulation and CNS tissue[77]. NVUs communicate in a process known as neurovascular coupling to ensure consistent blood flow in response to neuronal activity[77]. However, following brain injury, communication within the NVU can be disrupted, leading to inappropriate changes in cerebral blood flow and BBB dysfunction[77]. This disruption can result in protein and electrolyte leakage into the brain parenchyma, triggering downstream processes such as microglia activation, that persist long after the primary injury, potentially contributing to ongoing neuropathology[77].

The brain relies heavily on consistent cerebral blood flow (CBF) to function optimally, unlike other organs, as it cannot withstand prolonged blood supply shortages. CBF is intricately linked to neuronal activity and is regulated by cerebral autoregulation, which maintains cerebral perfusion pressure (CPP) within a specific range to safeguard neural tissues from ischemia and subsequent neurodegeneration[78]. CPP is primarily determined by the difference between mean arterial pressure and intracranial pressure and it is maintained between 70–90 mmHg in healthy patients[79]. Cerebral autoregulation involves several interconnected processes, including neurogenic, myogenic, vasogenic, and metabolic mechanisms, mediated by various cellular components such as endothelial cells, smooth muscle cells, neurons, and glial cells[57]. These mechanisms adjust CBF in response to changes in systemic blood pressure, with different brain regions exhibiting distinct regulatory patterns[57].

TBI can impair cerebral autoregulation, which is vital during low systemic blood pressure scenarios, leading to diminished CBF[80]. Even mild TBIs (mTBI) can lead to cerebrovascular injury[81]. While cerebral autoregulation can maintain CPP between a wide range of pressures, neurotrauma can hinder this ability. This can manifest as symptoms ranging from a headache to chronic seizures or neuroendocrine abnormalities[82]. TBI can induce functional disruptions and neurodegenerative changes that impact CBF, potentially leading to lasting alterations in CBF regulation and post-traumatic complications.

Cerebral vascular dysfunction can arise from direct injury to vascular components or from secondary cascades initiated post-injury; as a result, cerebral vascular dysfunction can manifest either before or after neuronal damage in TBIs[83]. Reductions in CBF and microvascular circulation can lead to the formation of microthrombi, causing tissue hypoxia[77]. Microthrombi aggregation can then lead to secondary injuries such as hematoma formation and edema[77]. Vasogenic edema can cause hemispheric expansion and midline shift[77]. These effects of microvasculature disturbances, endothelial irregularities, dysmorphic capillaries, and disruption of pericytes and perivascular astrocytes, are seen even when models are used to simulate mTBIs[77].

Additionally, cerebrovascular reactivity (CVR) is a dynamic assessment of microvascular function that can serve as a sensitive biomarker of traumatic cerebrovascular injury (TCVI) in individuals with chronic moderate to severe TBIs[84]. CVR can be assessed with either functional near-infrared spectroscopy (fNIRS) or functional magnetic resonance imaging (fMRI), each offering its own set of advantages and drawbacks[84]. While fMRI stands as the benchmark due to its high resolution and compatibility with structural imaging, fNIRS presents superior temporal resolution, lower cost, and greater ease of use in outpatient settings[84]. Employing either imaging modality for CVR assessment not only holds potential as an additional diagnostic tool for evaluating TBI, but also emerges as a promising predictive and pharmacodynamic biomarker for interventions aimed at addressing TCVI[84].

Additionally, vascular risk factors such as hypertension, diabetes, hyperlipidemia, and especially smoking, lead to worse outcomes after TBI[85]. This necessitates aggressive treatment to improve patient outcomes for those with these risk factors[85] (Figure 3).

REPAIR AND RECOVERY AFTER TRAUMATIC BRAIN INJURY AND SPINAL CORD INJURY

As shown through microdialysis, positron emission tomography, and magnetic resonance spectroscopy studies, TBIs can trigger a state of hypermetabolism characterized by increased glucose demand following biochemical brain injury, leading to neurotransmitter release and subsequent cellular responses[86]. This hyperactivity, aimed at restoring cellular and ionic homeostasis against progressing neuronal injury, can induce apoptotic events and mitochondrial impairment [86]. This causes a decrease in available energy for the body, which combined with the pre-existing microvascular ischemia, can lead to poor patient recovery[86]. Therefore, recovery after TBI is a complex process influenced by numerous factors, including the severity and type of injury or stress, vascular anatomy, comorbidities, access to medical care and rehabilitation, as well as social support networks[87].

In TBI, the inherent mechanisms responsible for cerebrovascular repair remain incompletely understood. However, studies have shown that hypoxia-inducible factor 1α (HIF-1) plays a pivotal role in both natural recuperation and safeguarding against neurological damage following TBI[88]. HIF-1 is a vital regulator of homeostasis that can induce angiogenesis, erythropoiesis, as well as anti-apoptotic cascades[88,89].

Additionally, vascular endothelial growth factor-A (VEGF-A) is also released, increasing angiogenesis, vascular permeability, and vasogenic edema[90]. Moreover, it has been shown that veterans with blast-related mTBIs show persistently elevated levels of plasma VEGF-A, indicating continued cerebrovascular dysfunction following injury[91]. Animal studies have shown that levels of VEGF-A reach their highest levels at 24 hours after a TBI. The same study showed that bevacizumab, a common antitumor drug, can be given immediately after TBI to suppress VEGF-A expression and decrease cerebral edema[90].

Reducing cerebral edema is a key factor in the treatment of TBI. For example, the astrocytic water channel AQP-4 system plays a critical role in brain edema and transport across the BBB[92]. Animal studies have shown that minocycline, an antibiotic, could be used in a vascular-protective fashion against TBI because it reduced AQP-4 levels, thereby decreasing cerebral edema to optimize BBB integrity and astrocyte function[92]. Minocycline was also shown to be neuroprotective by reducing apoptosis of neurons and inflammation[92]. In the same way, stromal vascular fraction was also shown to ameliorate motor skills and slow memory regression in animals after TBI[93]. Yet another study showed a promising approach for TBI treatment with a novel biological scaffold containing heparin, collagen, and VEGF that could improve motor and cognitive function by generating an optimal microenvironment for the regeneration of injured nerve tissue[94].

VEGF-C is another of the vascular endothelial growth factors, which regulates microglia polarization and reduces cell apoptosis. Administration of VEGF-C has been shown to improve motor and neurologic function after TBI in animal models[95]. Administration of VEGI recombinant protein also showed similar results[96].

Moreover, these growth factors have been used as biomarkers to monitor outcomes in patients following TBI in the Transforming Research and Clinical Knowledge in TBI Pilot Study. This study showed that higher levels of thrombomodulin, angiopoietin-2, von Willebrand factor, and P-selectin were associated with more critical injuries while higher levels of angiopoietin-1, VEGF-C, and basic fibroblast growth factor were associated with less critical injuries[97].

Lastly, exercise has been shown to improve balance and walking abilities after neurotrauma[98]. Exercise can be done with physical therapists or even with robotic devices or virtual reality to progress neurorehabilitation[98].

While many animal studies over the years have initially shown promising results, later translation in human trials has often been less impressive[99,100]. This highlights the continued importance of pursuing innovative, new models and species that better capture human biology and choosing models that are best suited for the intricacies of the individual study.

CONCLUSION

The future of treatment options and the direction of future research for neurotrauma are poised for significant advancements aimed at improving patient outcomes and quality of life. Emerging therapeutic avenues are expected to focus on reducing cerebral edema, decreasing blood-brain barrier breakdown, and decreasing neuronal cell death. Additionally, there will be a growing emphasis on multidisciplinary collaboration, bringing together experts from various fields including neuroscience, neurology, neurosurgery, rehabilitation medicine, and bioengineering.

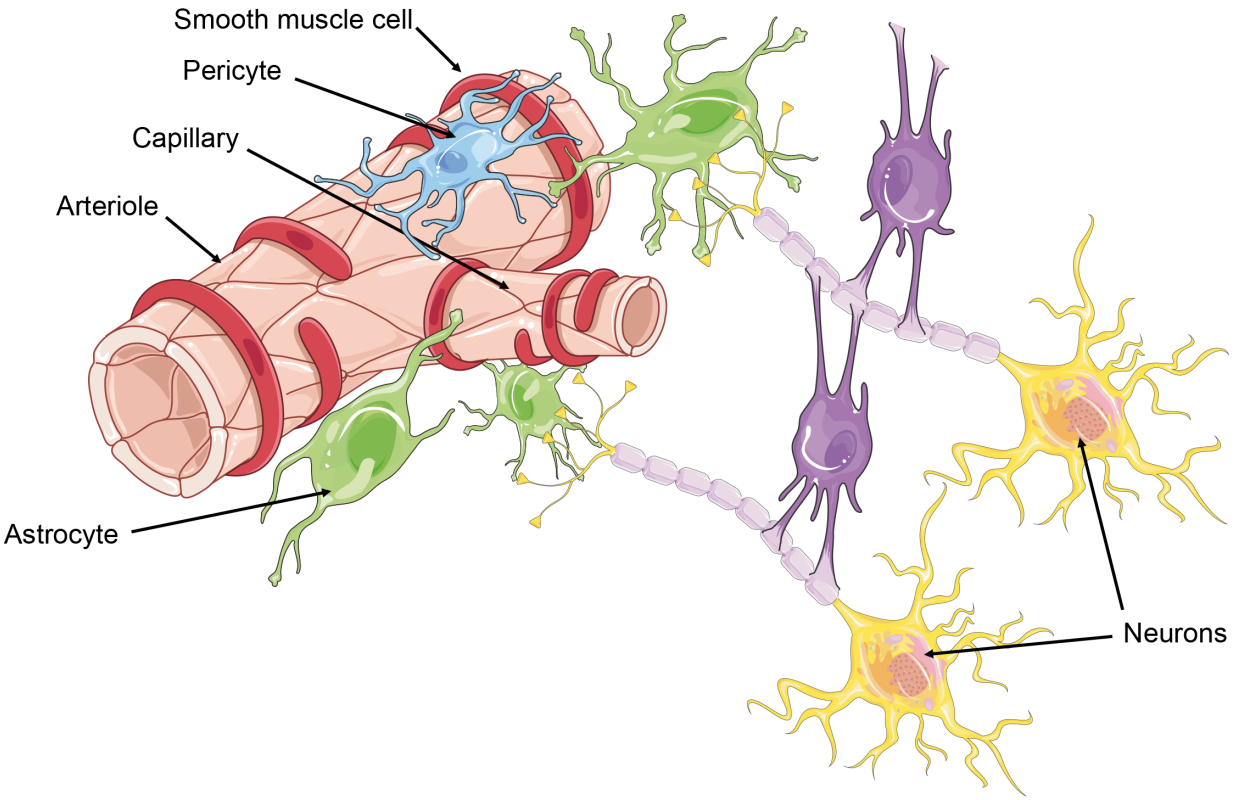

Figure 3 The neurovascular unit is a network created by the communication between pericytes, neurons, smooth muscle, and endothelial cells. Parts of the figure were drawn by using modified pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

The development of novel pharmacological agents targeting specific molecular pathways implicated in neuroinflammation, excitotoxicity, and neuroregeneration holds promise for more effective treatments. These therapies may include neuroprotective agents, anti-inflammatory drugs, stem cell therapies, and gene therapies, among others.

Moreover, the integration of neurostimulation technologies, including transcranial magnetic stimulation, deep brain stimulation, and non-invasive brain stimulation techniques, offers exciting prospects for modulating neuronal activity and promoting neural plasticity to aid in recovery and rehabilitation post-neurotrauma. Additionally, advancements in neurorehabilitation strategies, such as robot-assisted therapy, virtual reality training, and brain-computer interfaces, are expected to play a crucial role in facilitating functional recovery and enhancing patient independence.

In terms of research directions, there will be a continued focus on elucidating the underlying pathophysiology of neurotrauma, including the complex interplay between genetic, environmental, and lifestyle factors. Large-scale prospective clinical studies and translational research efforts will be essential for validating novel therapeutic approaches and establishing evidence-based guidelines for optimal patient management. Furthermore, initiatives aimed at enhancing public awareness, education, and prevention strategies for neurotrauma will remain paramount in reducing the burden of these devastating injuries on individuals and society.

Overall, the future of treatment options and research directions for neurotrauma holds great promise, driven by advancements in technology, interdisciplinary collaboration, and a deeper understanding of the underlying mechanisms of brain injury and repair. These efforts aim to improve outcomes, enhance quality of life, and ultimately transform the landscape of neurotrauma care.

FOOTNOTES

Author contributions: Willman J worked with the other authors in conceptualization. He planned the structure of the paper, orchestrated the first draft, and wrote significant portions of the first draft. He was a co-corresponding author and the primary editor; Kurian AL contributed to the conceptualization and wrote significant portions of the first draft; Lucke-Wold B contributed to the conceptualization and helped orchestrate the project. He was a co-corresponding author. He provided senior oversight and quality review.

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MINIREVIEWS

Vascular complications of liver abscess: A literature review

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Abstract

Extensive vascular network and proximity to the gastrointestinal tract make the liver susceptible to abscess formation. While pyogenic liver abscesses account for the majority of liver abscesses in the Western world, amebic liver abscesses are more prevalent in tropical and developing nations. Most liver abscesses heal without complications. However, various vascular complications can occur in these patients, including compression of the inferior vena cava, thrombosis of the portal vein and/or hepatic veins, hepatic artery pseudoaneurysm, direct rupture into major vessels or the pericardium, and biliovascular fistula. These complications can present significant clinical challenges due to the potential for haemorrhage, ischemia, and systemic embolism, thereby increasing the risk of morbidity and mortality. Mechanical compression, flow stasis, inflammation, endothelial injury, and direct invasion are some of the proposed mechanisms that can cause vascular complications in the setting of a liver abscess. For the diagnosis, thorough assessment, and therapeutic planning of vascular complications, more sophisticated imaging techniques such as multidetector computed tomography angiography or magnetic resonance angiography may be necessary. Although most vascular complications resolve with abscess treatment alone, additional interventions may be required based on the nature, severity, and course of the complications. This article aims to provide a systematic update on the spectrum of vascular complications of liver abscesses, offering insights into their pathogenesis, diagnosis, and management strategies.

Key Words: Liver abscess; Pylephlebitis; Venous thrombosis; Pseudoaneurysm; Portal cavernoma; Inferior vena cava obstruction

Core Tip: Liver abscess is a focal infection of hepatic parenchyma caused by various bacteria and the protozoa *Entamoeba histolytica*. It poses a considerable risk of vascular complications, including venous thrombosis, arterial pseudoaneurysms, thromboembolism, and biliary communication, as these complications can cause ischemia and hemorrhages, presenting significant challenges to clinicians. This review summarizes the existing literature on these lesser-known complications, providing insights into their magnitude, mechanistic pathogenesis, diagnosis, and management strategies.

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INTRODUCTION

A liver abscess (LA) is a significant infectious complication of the liver parenchyma that requires accurate diagnosis and targeted treatment. Most LAs are classified as amebic liver abscesses (ALA), caused by the anaerobic protozoan *Entamoeba histolytica*, or pyogenic liver abscesses (PLA), caused by various bacteria. Rarely, an LA can be of fungal or tubercular origin. ALA is usually a non-suppurative liver infection with thick brown, odorless, and sterile acellular debris[1]. In contrast, PLA is a pus-filled, suppurative liver infection that is usually culture-positive. PLA is mostly polymicrobial with certain organisms, including Klebsiella, Escherichia coli, Anaerobes, Streptococcus, and Staphylococcus being more frequently noted[2]. There has been a perceptible global trend in the incidence of LA[3]. Certain conditions, such as diabetes mellitus, male gender, advanced age, and impaired immune systems, render individuals more susceptible to LA [2]. The incidence and forms of LA differ geographically, with higher ALA prevalence in tropical regions and developing countries such as the Indian subcontinent, Africa, Central and South America, and Mexico[4]. ALA constitutes over 80% of all LA cases in India[5]. The predominant form of LA in the Western world is PLA, with an incidence rate of 2.3 per 100000 population in North America[6]. Males over 60 have a higher prevalence of PLA.

The liver is vulnerable to both ALA and PLA due to its complex vascular network and close relationship with the gastrointestinal (GI) tract. The dual blood supply of the liver, comprising the portal vein (PV) and hepatic artery (HA), is unique among visceral organs[7]. The liver's proximity to many vessels increases its vulnerability to the hematogenous dissemination of infections and potential vascular complications[8]. These complications arising from LA encompass a wide spectrum, including vascular thrombosis, thromboembolism, rupture into large vessels, and pseudoaneurysm, underscoring the intricacy of the condition. Pulmonary thromboembolism and trans-diaphragmatic rupture into the heart, resulting in cardiac tamponade, are among LA's potentially fatal complications[9-12]. Patients with PLA and ALA have both been reported to have vascular complications. In a large study from India, vascular complications were reported in 93 of 1630 LA patients (5.7%)[13]. However, up to 69% of ALA patients had venous thrombosis, in a recent study specifically designed to identify vascular complications using a multidetector computed tomography (CT) scan [14]. Several proposed mechanisms can lead to vascular complications in the context of LAs, including vascular compression, flow stasis, inflammation, endothelial damage, and direct invasion[4,15-17]. Further, chronic inflammation can weaken the HA wall, making it vulnerable to the development of hepatic artery pseudoaneurysm (HAPA) and its eventual rupture[18,19]. This article aims to provide an update on the spectrum of vascular complications of LA, including their pathophysiology, diagnostic approach, and therapeutic considerations. A systematic literature search up to February 2024 was performed using PubMed and Google Scholar database for the purpose of this article.

VASCULAR ANATOMY OF THE LIVER IN RELEVANCE TO LA

The development of LA is significantly influenced by the liver's vascular architecture. The liver is divided into eight segments, each with a separate vascular supply. Based on the blood supply to particular hepatic segments, LA may be the site of localization. Comprehending this segmental blood flow facilitates the understanding of the mechanisms by which infections enter the liver parenchyma. The amebic trophozoites colonize the cecum, invade the mucosa, and enter the liver through the portal circulation to cause ALA[4]. The right lobe of the liver is more frequently affected by ALA because the superior mesenteric vein, which drains the area of the intestine where trophozoites invade, is the main conduit for portal blood flow to the liver. In the case of PLA, where bacterial invasion can occur through the venous, arterial, or biliary systems, such lobar preference is not shown. Generally, biliary tract infections or ascending cholangitis cause right lobe PLA, whereas diverticulitis or colonic cancer can cause PLA in the left lobe[2]. The inferior vena cava (IVC) is more susceptible to compression and thrombosis from the LA of the caudate lobe due to its proximity[20]. The liver is an important defense against microbial invasion. Therefore, bacteria may evade the hepatic filtration mechanisms in situations of portal vein thrombosis (PVT), raising the risk of infections, including PLA[2].

MECHANISMS OF VASCULAR INVOLVEMENT IN LA

Several factors contribute to vascular involvement in LA, including the followings:

Hemodynamic changes due to compression

An expanding LA exerts pressure on nearby vessels, compromising their integrity and functionality, leading to alterations in blood flow[16,21]. The resultant pockets of stagnant blood can foster the development of thrombi. These thrombi can further impair blood flow and affect the cellular function and viability of the hepatic cells around the LA by preventing the delivery of oxygen and nutrients[22].

Inflammation and endothelial damage

Within the liver parenchyma, microbial invasion sets off a series of inflammatory reactions. The inflammatory mediators generated in response impact the surrounding vasculature, besides the abscess site. Vascular endothelial cells are essential for maintaining structural integrity. The inflammatory processes sparked by microbial invasion cause endothelial injury in nearby blood vessels, jeopardizing the structural integrity of vessels[23,24]. A pro-thrombotic surface created by damaged endothelial cells encourages platelet adhesion and activation. The coagulation cascade that leads to thrombus formation is initiated when platelets attach to the exposed subendothelial matrix[25]. The thrombus can impede blood flow in the involved vessels, worsening the compromised blood flow. In a recent study, 69% of ALA patients had venous thrombosis, and 53% showed a zone of perilesional ischemia[14]. Despite extensive thrombosis of the IVC and HV, underlying thrombophilia states were found negative in a study, highlighting the thrombogenic potential of ALA [26]. Besides thrombotic complications, inflammatory damage to nearby arteries may cause the accumulation of blood between tunica media and tunica adventitia of the arterial wall, leading to the formation of a pseudoaneurysm[18,19].

Direct invasion

Rupture into nearby structures is one of the most common complications of LA[4]. LAs of the left lobe and the caudate lobe are more vulnerable to cardiovascular complications due to their proximity to the heart and major vessels. ALA has been reported to directly invade the IVC[15,17]. Concomitant injury to the bile ducts and HV may cause a biliovascular fistula, which raises serum bilirubin levels rapidly[27].

SPECTRUM OF VASCULAR COMPLICATIONS AND CLINICAL PRESENTATION

The spectrum of vascular complications in LA patients is depicted in Figure 1. It includes the following:

Vascular compression

The complication due to vascular compression is more common with large LAs located in the caudate lobe (Figure 2). Huddle *et al*[16] and Sharma *et al*[21] reported a case of caudate lobe ALA causing extrinsic compression of the IVC without evidence of thrombosis. Mehrotra *et al*[28] reported a large staphylococcal PLA causing IVC compression and presenting as acute Budd-Chiari syndrome (BCS). Karadag *et al*[29] have also reported a case of PLA compressing the IVC and HVs, causing acute BCS.

Venous thrombosis

Venous thrombosis contributes to the intricate cardiovascular landscape associated with LA (Figure 3). The reported frequency of thrombotic consequences varies widely, from 3.7% to as high as 69%[14,28,30]. Venous thrombosis has been reported in LAs of both amebic and pyogenic origin (Tables 1 and 2).

Venous thrombosis in ALA patients: Krishnan *et al*[15] found IVC thrombosis in 8% of cases and HVT in all but one of the 95 ALA patients in a comprehensive autopsy study. In another autopsy series, Aikat *et al*[31] reported PVT in 27.5%, HVT in 29.5%, and IVC thrombosis in 4% of ALA cases. Sarda *et al*[32] reported three cases of ALA-induced IVC obstruction that was resolved after percutaneous drainage and antibiotic treatment. Three cases of ALA extending into the IVC and causing its thrombosis were recently reported by Marak *et al*[17]. Hodkinson *et al*[33] reported another case of a 50-year-old man with ALA who developed an IVC thrombus that spread to the right atrium. Sodhi *et al*[34] reported a 57-year-old man whose ALA was complicated by HVT and IVC thrombosis.

Venous thrombosis in PLA patients: In a study by Syed *et al*[35], 28 out of 67 patients (42%) with PLA had venous thrombosis. PVT was present in 24%, HVT in 22%, and combined PVT + HVT in 4% of patients. Venous thrombosis resolved in 37% of 27 patients after 6 months and persisted in 63% during the 3- to 38-month follow-up period. Yang *et al* [30], in a retrospective analysis of 81 PLA patients, reported PVT in three patients (3.7%), and one patient also had extrinsic compression of the IVC. In a study, PLA due to Klebsiella pneumoniae was identified as the most common (37%) cause of thrombophlebitis of the portal venous system (pylephlebitis)[36]. PLA due to various other bacterial causes such as *Lactococcus lactis*, *Fusobacterium nucleatum*, and *Clostridium clostridioforme* has been reported to be complicated by PVT[37-39]. In a retrospective analysis of 169 patients with Klebsiella pneumoniae-associated PLA, Molton *et al*[40] found that 53 patients (31.4%) had thrombophlebitis of the PV or HV. In follow-up scans, 73% (30/49) of patients showed spontaneous recanalization in a mean duration of 44 days. Thrombosis of the cerebral venous sinus and superior mesenteric vein has also been reported in association with PLA[41,42].

Table 1 The vascular thrombotic complications in association with amebic liver abscess

Ref.	Study type	Vascular complication	Age /gender	LA size & site	Treatment	Outcomes
Sarda *et al*[32], 2010, India	Case series, *n* = 3	IVC thrombosis	21, 24, and 61 years/M	Large, caudate lobe	Antibiotics and PD	Complete resolution
Jesrani *et al*[43], 2020, India	Case report	PTE	26 years/M	Large, segment VIII	Antibiotics, PD, and anticoagulation	Stable clinical improvement
Sodhi *et al*[34], 2007, India	Case report	Hepatic vein and IVC thrombosis	57 years/M	Large, right lobe	Antibiotics, PD, and anticoagulation	Continued improvement
Martin *et al*[26], 2017, Canada	Case report	IVC and hepatic vein thrombosis	43 years/M	Large, caudate lobe	Antibiotics	Stable clinical improvement
Gupta *et al*[72], 2013, India	Case report	IVC thrombosis	6 years/M	Small, left lobe	Antibiotics + surgical thrombectomy	Complete resolution
Khan *et al*[73], 2009, Pakistan	Case report	IVC and right atrium thrombus	46 years/M	Large, right lobe	Antibiotics, PD, antico-agulation, and surgical thrombectomy	Complete recovery
Prendki *et al*[9], 2011, France	Case report	IVC and right atrial thrombosis, and PTE	23 years/M	Large, right lobe	Antibiotics, PD, and anticoagulation	Continued clinical improvement
McKenzie *et al* [10], 2015, United States	Case report	IVC and HV thrombosis, PTE	43 years/M	Large, left lobe	Antibiotics and antico-agulation	Stable clinical improvement
Goel *et al*[53], 2020, India	Case report	Bilhaemia, PVT, and HVT	64 years/M	Large, segment IV	Antibiotics, PD, and anticoagulation + biliary stenting	Complete improvement
Marak *et al*[17], 2023, India	Case series, *n* = 3	IVC thrombosis	38, 55 & 56 years/M	Large, both lobe	Antibiotics and PD	Stable improvement
Siddiqui *et al* [64], 2013, India	Case report	IVC and right atrial thrombus	2 years/M	Large, segment IV/VIII	Antibiotics, surgery, anticoagulation	Complete resolution of abscess
Ray *et al*[70], 2012, India	Case report	IVC thrombosis	47 years/M	Large, right lobe	Antibiotics and PD	Uneventful recovery
Méchaï *et al*[65], 2009, France	Case report	HVT (Budd-Chiari syndrome)	87 years/M	Large, right lobe	Antibiotics, PD, and anticoagulation	Progressive recovery
Thati and Nagral[66], 2014, India	Case report	IVC thrombosis with PTE	50 years/M	Large, segment VIII	Antibiotics, PD, and anticoagulation	Complete improvement
Priyadarshi *et al* [14], 2020, India	Prospective cohort, *n* = 62	Venous thrombosis in 43 (69%), including PVT, HVT and IVC thrombosis	Mean age 37 years/M 95%	Mean size 95 cm, both lobes	Antibiotics and PD	Partial resolution of thrombus and segmental atrophy of liver in 5 patients after 2 months

IVC: Inferior vena cava; PVT: Portal vein thrombosis; HVT: Hepatic vein thrombosis; PD: Percutaneous drainage; PTE: Pulmonary thromboembolism.

Clinical consequences of vascular obstruction

Thrombosis of segmental hepatic vessels appears to aggravate the severity of LA. Priyadarshi *et al*[14] found that hepatic ischemia caused by venous thrombosis increased the severity of LA, and more patients with hepatic ischemia experienced an aggressive clinical course necessitating interventional therapy. LA patients with IVC thrombosis are at risk of thromboembolic phenomena. Several studies, including those by Prendki *et al*[9], McKenzie *et al*[10], and Jesrani *et al*[43], have reported cases of ALA complicated by pulmonary thromboembolism. A high index of suspicion is required to diagnose these complications in LA patients who might have hemodynamic instability and respiratory distress. Thrombosis of the HV and IVC may introduce additional signs such as pedal edema, ascites, and hepatomegaly, indicating possible venous congestion and impaired venous return. Thus, LA can rarely result in the development of secondary BCS. The development of portal hypertension poses an additional challenge and reflects the systemic impact of a complicated LA. There are many reports of neonatal PLA complicated by PVT with subsequent formation of portal cavernoma[44-46]. Shah *et al*[44] reported the appearance of PVT in a neonate after 16 days of treatment for LA, who subsequently developed portal hypertension. Aggarwal *et al*[45] and Sethi *et al*[46] also reported PVT and cavernoma in association with neonatal PLA. One key clinical indicator that points to the presence of PVT in patients with LA is unexplained abdominal pain, particularly if it is severe and persistent. Patients with pylephlebitis may develop severe sepsis, including septic shock and decreased cognitive function.

Table 2 The vascular thrombotic complications in association with pyogenic liver abscess

Ref.	Study, patient (s)	Types of vascular complications	Demographics	PLA size and location	Treatment	Outcomes
Syed *et al*[35], 2007, Canada	Retrospective study, PLA, *n* = 67	PVT (24%) and HVT (22%)	Mean age 55 years, male 80%	Mean, 8.5 cm, mainly right lobe	Standard treatment, detail NA	Thrombosis resolved in 37% within 6 months
Trad *et al*[67], 2022, United States	Case report, PLA	Pylephlebitis (PVT)	49 years male	5 cm × 3.5 cm, right lobe	Antibiotics and anticoagulation	Complete recovery
Molton *et al* [40], 2015 Singapore	Retrospective study, *n* = 169 KLA	Regional vein thrombosis	Median age 58 years, 71% male	Mean abscess size 67cm, both lobe	Antibiotics, drainage in 77% patients, anticoagulation in one patient	Complete recanalization in 73.2% cases, death in 3.6% patients
Wang *et al*[36], 2013 Taiwan	Retrospective study, *n* = 35, KLA	Pylephlebitis	Median age 57, 83% male	NA	Antibiotics	Longer hospital stay, but no mortality
Kubo *et al*[41], 2017, Japan	Case report, PLA (Morganella morganii)	PVT and Superior mesenteric vein thrombosis	59 years/male	PLA in segment VIII	Antibiotics, anticoagulants and surgery for diverticulitis	Stable clinical improvement
Güz *et al*[37], 2006, Turkey	Case report, PLA (Lactococcus lactis)	PVT	26 years/male	17 cm × 11 cm × 11 cm PLA, right lobe	Antibiotics, PD, and anticoagulants	Persistent PVT till 6 months
Shah and Bhatnagar[44], 2009, India	Case report, PLA	PVT and portal cavernoma	20-day neonate	5.1 cm × 5.8 cm PLA, right lobe	Antibiotics, surgical drainage	Stable improvement
Aggarwal *et al* [45], 2003, India	Case report, PLA (Staphylococcus aureus)	PVT and portal cavernoma	28-day, neonate	5 cm × 4 cm PLA, right lobe	Antibiotics	Stable improvement
Etienne *et al* [68], 2001, Australia	Case report, PLA (Fusobacterium nucleatum)	Pylephlebitis (PVT)	68 years/male	3-cm × 5-cm PLA, right lobe	IV antibiotics, anticoagulants	Complete resolution
Zhou *et al*[42], 2022, China	Case report, KLA	Cerebral venous sinus thrombosis	54 years/male	Multiple abscess, largest 59 mm × 49 mm, right lobe	Antibiotics, anticoagulants	Clinical improvement, no significant change in cerebral sinus thrombosis
Ogah *et al*[39], 2012, United Kingdom	Case report, PLA (Clostridium clostridioforme)	PVT	6 years/F	Multiple PLA	Antibiotics and PD	Complete recovery
Bagri *et al*[56], 2013, India	Case report, PLA	IVC and right atrial thrombosis	2 years 9 month boy	5 cm × 4.8 cm × 5.8 cm, right lobe	Antibiotics and surgery	Gradual complete improvement
Linsen *et al*[69], 2023, Netherlands	Case report, PLA (*Escherichia coli* and *Fusobacteriumspp*)	Pylephlebitis	42 years/male	Multiple abscesses, right lobe	Antibiotics, anticoagulants	Gradual improvement with complete resolution of abscess
Mehrotra *et al* [28], 1991, India	Case report, PLA (Staphylococcus aureus)	Acute Budd Chiari, IVC thrombosis	6 years/male	Right lobe liver abscess	Antibiotics and Surgical drainage	Complete recovery
Maffiolo *et al* [71], 2006, France	Case series, KLA	Thrombophlebitis of HV	42 and 55, male	Multiple abscesses right lobe	Antibiotics and PD	Complete improvement

KLA: Klebsiella liver abscess, IVC: Inferior vena cava; PVT: Portal vein thrombosis; HVT: Hepatic vein thrombosis; PD: Percutaneous drainage; PLA: Pyogenic liver abscess.

HAPA

HAPA, although uncommon, are the second most prevalent type of pseudoaneurysm involving the splanchnic artery. They are usually extrahepatic in location (75%) and traumatic in origin[47]. Nonetheless, HAPA, in association with LA, are generally intrahepatic and can also be intracavitary (Figure 4). HAPA have been reported more often in association with ALA than PLA (Table 3). The first incidence of HAPA linked to an ALA was reported by Gopanpallikar *et al*[48] in 1997. Silvestri *et al*[49] reviewed 6 cases of HAPA associated with ALA. The mean age of patients was 44.8 ± 8 years, and all were male. The most common presentation was fever, abdominal pain, and GI bleeding. The aneurysm ruptured in two cases, while it regressed spontaneously in two others after treating ALA. With available follow-up data in 5 patients, all had uneventful recoveries. Qi *et al*[50] reported HAPA in association with PLA due to Listeria monocytogenes in a 50-

Table 3 Hepatic artery pseudoaneurysm associated with amebic and pyogenic liver abscess

Ref.	Study type	Age/gender	LA type	Complication	Treatment	Outcomes
Silvestri and Ngasala [49], 2022, Tanzania	Case review, *n* = 6	Mean age 448 years	ALA	HAPA	IV antibiotics and aneurysm embolization in 3 cases	Uneventful recovery in 5 patients
Priyadarshi *et al*[19], 2019, India	Case report	52 years/M	ALA	Right HAPA (10 mm) with hemobilia	Antibiotics and PD	Complete resolution
Tacconi *et al*[75], 2009, Italy	Case report	31 years/M	ALA	Right HAPA (15 mm)	Antibiotics and needle aspiration of ALA	Complete resolution
Yadav *et al*[51], 2015, India	Case report	45 years/M	ALA	HAPA with hemobilia	Antibiotics, PD of ALA and percutaneous glue embolization	Uneventful recovery
Kang *et al*[18], 2006, India	Case report	58 years/F	ALA	Right HAPA (15 mm) with rupture into abscess	PD of ALA + Coil embolization	Complete resolution
Qi *et al*[50], 2023, United States	Case report	50 years/F	PLA	HAPA	IV antibiotics and PD	Complete improvement
Lee *et al*[74], 2020, Korea	Case report	80 years/M	PLA	HAPA	IV antibiotics, PD and percutaneous embolization	Complete resolution

ALA: Amebic liver abscess; PLA: Pyogenic liver abscess; HAPA: Hepatic artery pseudoaneurysm; PD: Percutaneous drainage.

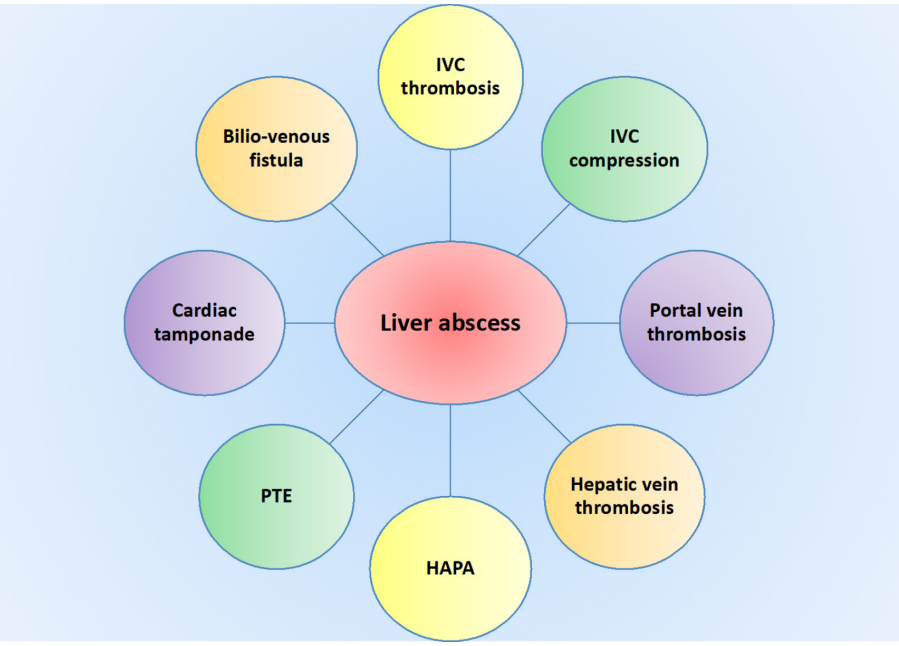

Figure 1 Spectrum of vascular complications associated with liver abscess. IVC: Inferior vena cava; HAPA: Hepatic artery pseudoaneurysm; PTE: Pulmonary thromboembolism.

year-old woman. While HAPA may be asymptomatic in patients with LA, symptoms such as persistent abdominal pain, bleeding manifestations, or signs of hemodynamic instability should raise suspicions about this complication. Rupture of the HAPA into the biliary system can lead to hemobilia presenting as GI bleeding[18,51]. Importantly, in patients with ALA, concurrent ileo-colonic ulcerations caused by amebic trophozoites frequently result in GI hemorrhage[52]. Early detection and prompt management of HAPA are important, considering that its complications are catastrophic.

Other vascular complications

On rare occasions, LA can lead to an intrahepatic connection between the biliary and venous systems, resulting in the mixing of bile and contents of the LA with blood in low-pressure intrahepatic veins. This leads to a rapid increase in the levels of bilirubin and bile acids in serum. Thus, biliovascular fistula is a unique and uncommon consequence of LA that may have significant clinical implications[27,53]. Singh *et al*[27] described the occurrence of biliovascular fistula in 12 ALA patients with hyperbilirubinemia. Interestingly, following biliary diversion with nasobiliary drainage, the hyperbilirubinemia in these patients returned to normal.

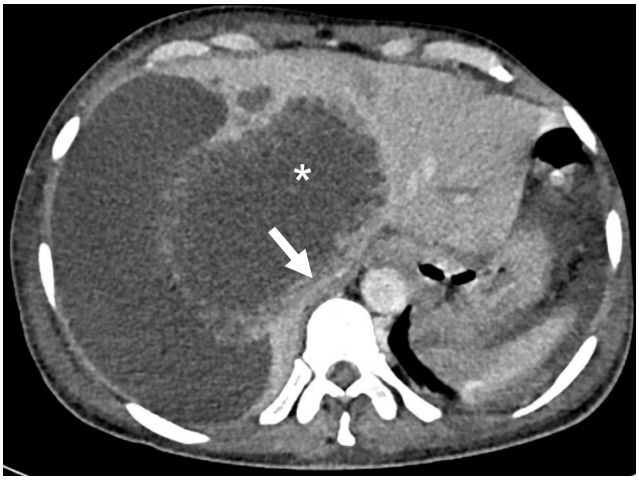

Figure 2 Axial contrast-enhanced computed tomography image showing a large ruptured amebic liver abscess (asterisk) in the caudate lobe, exerting pressure on the inferior vena cava (arrow). Note the fluid collection in perihepatic space resulting from the ruptured abscess.

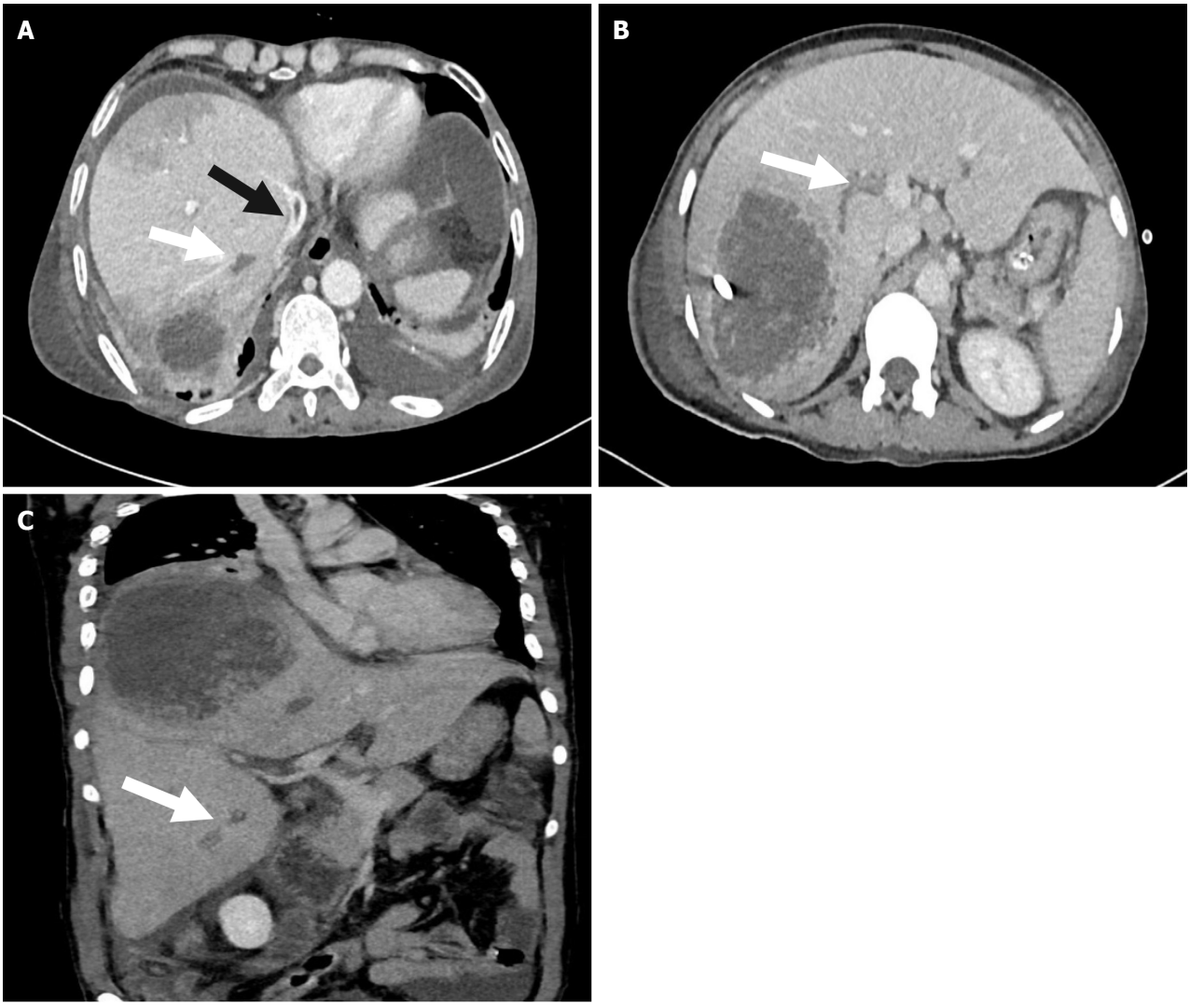

Figure 3 Venous thrombosis in associations with liver abscess. A: Axial contrast-enhanced computed tomography (CT) imaging illustrates the presence of thrombosis within the inferior vena cava (black arrow) and the right hepatic vein (white arrow) in a patient with abscess in right lobe of liver; B: Axial contrast-enhanced CT scan demonstrates the presence of a thrombus within the right posterior segmental branch of the right portal vein in a patient with liver abscess; C: Coronal contrast-enhanced CT imaging depicts thrombosis occurring in the segmental branch of the right portal vein in a patient with liver abscess.

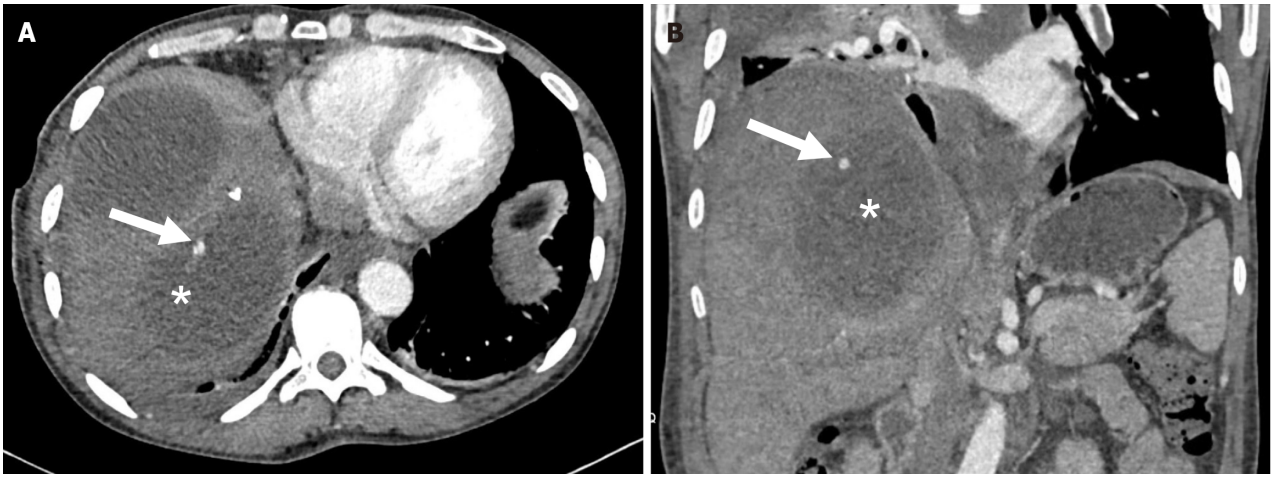

Figure 4 Computed tomography scan image of hepatic artery pseudoaneurysm in association with liver abscess. A: Axial image demonstrating a small aneurysm (arrow) originating from a peripheral branch of the right hepatic artery within the abscess cavity (asterisk); B: Coronal computed tomography image of the same patient demonstrating the hepatic artery pseudoaneurysm.

The heart is a vital component of the vascular system. Due to its proximity to the liver's left lobe, the heart may get involved in complicated left lobe LA. As rupture is a common complication of ALA, cardiac tamponade may result from the rupture of the left lobe of ALA into the pericardium[35,36]. PLA due to Actinomyces, which is a gram-positive anaerobic to microaerophilic bacterium, has been associated with purulent pericarditis with cardiac tamponade[54,55]. The presence of dyspnea, tachycardia, hypotension, and pulsus paradoxus can raise suspicions about this life-threatening complication of LA. Early diagnosis of this condition is necessary to avoid adverse outcomes. Rarely, right heart failure can occur in patients with LA due to a right atrial thrombus[56].

MANAGEMENT ISSUES: DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS

The initial presentation of LA with vascular involvement may be similar to that of uncomplicated LA. However, when LA patients develop persistent or worsening abdominal symptoms, ascites or pedal edema, gastrointestinal bleeding, dyspnea, or hemodynamic instability, vascular complications should be suspected. Appropriate imaging modalities should be used to diagnose these complications to enable timely intervention and improved patient outcomes. Doppler ultrasound can be the initial imaging modality to diagnose PVT. It has the advantages of being non-invasive, widely available, and good sensitivity to detect flow abnormalities in the PV. However, its role may be limited in patients with obesity or extensive thrombosis. More sophisticated imaging methods like multidetector CT angiography and magnetic resonance angiography provide better diagnostic precision and spatial resolution for identifying PVT and/or HVT and evaluating their severity and associated complications[57,58]. By providing a thorough assessment of collateral circulation, vascular patency, and cavernous changes, these modalities can aid in prognostication and therapeutic decision-making. Regarding HAPA, CT angiography is valuable for detecting, characterizing, and guiding treatment decisions[19,51]. Contrast-enhanced ultrasonography (CEUS) is a valuable diagnostic tool for LAs. It can also be used to differentiate LAs from other liver masses, characterize LAs, which may help with treatment decisions, and guide percutaneous catheter or needle drainage[59,60]. On CEUS, LAs commonly exhibit rim enhancement, a nonenhanced central necrotic region, enhanced internal septa, and transiently hyperenhanced liver parenchyma surrounding the lesions[61]. Treatment under Sonovue CEUS is associated with faster recovery, better treatment response, and a lower risk of complications in PLA patients[59].

Vascular complications of LA are managed through a multidisciplinary approach that considers multiple host- and disease-related factors. To navigate the intricacies of this clinical circumstance and provide optimal patient care, hepatologists, interventional radiologists, and surgeons must collaborate. Prompt initiation of antibiotic therapy targeting probable microorganisms is essential to treat the underlying abscess; typically, drugs like metronidazole are combined with cephalosporins or fluoroquinolones.[59] Image-guided percutaneous catheter drainage (PCD) of the abscess is crucial to eliminate the infectious source. Drainage is important because it facilitates better penetration of antibiotics and clears necrotic material, bile, and blood clots that delay the abscess cavity healing[62]. The routine use of anticoagulant medication for venous thrombosis in the setting of LA continues to be debated. The benefits of preventing thrombus propagation must be weighed against the risk of hemorrhagic complications[63]. Anticoagulation therapy resolves venous thrombosis associated with both ALA[64-66] and PLA[67-69]. Nevertheless, many reports document spontaneous recanalization of vascular thrombosis after proper treatment of LA alone[30,63,70,71]. Surgical thrombectomy has also been performed in some cases; however, such aggressive treatment is often unnecessary[72,73]. Sarda *et al*[32] reported recanalization of IVC obstruction in three ALA patients treated with percutaneous drainage and antibiotic therapy. Molton *et al*[40] reported spontaneous recanalization of vascular thrombosis in the majority (73%) of affected PLA patients without anticoagulant therapy. This implies that the underlying abscess should be the focus of treatment, rather

than the thrombus. However, therapeutic anticoagulation should be considered in cases of severe IVC thrombosis, right atrial thrombus, or thromboembolism.

HAPA can be treated with endovascular embolization, surgical resection, or close observation. Due to its rarity and the paucity of knowledge thereof, there is still no consensus on the best treatment approach. Given the significant morbidity associated with surgical treatment, percutaneous trans-arterial embolization is currently recommended for intrahepatic aneurysms[18,51,74]. Metallic coils, non-absorbable polyvinyl alcohol particles, or liquid embolic agents like N-butyl cyanoacrylate are the most common types of embolic agents used. Coils are the most commonly used embolic agent when vascular anatomy is favorable. Nevertheless, with appropriate treatment of LA using antibiotics and PCD, spontaneous resolution of HAPA is possible[19,50,75]. Which patients should be chosen for expectant treatment is unclear. A small HAPA (< 2 cm) arising from the peripheral branch of the HA may resolve spontaneously[19]. Repeated ultrasonography with Doppler can help clinicians monitor these patients while adhering to expectant treatment. For patients with pericardial rupture of LA, immediate pericardiocentesis is the cornerstone of treatment[12]. LA complicated by biliovascular fistula may respond to biliary diversion using nasobiliary drainage[27].

Thus, many of vascular complications require care of only LA with antimicrobials and percutaneous drainage. Ultrasound guided percutaneous drainage of LA is quite safe procedure. No major complication related to PCD or needle aspiration have been reported in patients with either PLA or ALA[1,76-78]. The requirement of additional treatment will depend on the nature, severity and course of vascular complication.

UNUSUAL CAUSES OF LIVER ABSCESS

Occasional causes of LA include mycobacteria and fungi[79]. Sometimes, suppuration of cystic hepatic diseases, such as hydatid cysts, can also result in LA. In a cross-sectional study from India (n = 200), the etiology of LA was mycobacteria in 7.5% and candida in 1.5% of 200 consecutive LA patients[79]. Fungal liver abscesses can occur in onco-hematologic patients and hematopoietic stem cell transplantation recipients[80]. Generally, fungal liver infections are caused by Candida species. Little information is available about vascular involvement in fungal LA. Paccoud *et al*[81] reported a case of chronic LA with PVT caused by Candida. Liver involvement is possible in endemic areas of tuberculosis; however, the presentation of hepatic tuberculosis as focal LA is extremely uncommon[82,83]. In a study, tubercular LA was found in the left liver lobe and smear positive for acid-fast bacilli. PVT has also been associated with hepatic tuberculosis rarely[84,85]. These cases have been successfully treated with antituberculosis medications and an anticoagulant[85]. A hepatic hydatid cyst can sometimes masquerade as LA[86]. Particularly, secondary bacterial infection of a hydatid cyst makes it difficult to differentiate from a PLA. In a large series of hepatic hydatid cysts, suppuration occurred in 7 of 328 cases (2.1%)[87]. Although vascular involvement in the form of PVT and secondary BCS has been reported in cases of hepatic hydatid disease, no literature has specifically detailed this complication vis-a-vis an infected hydatid cyst [88-90].

CONCLUSION

Vascular complications due to LA occur with varying frequencies[14,19,28,30,91]. They include mainly thrombosis of PV, HV, IVC, and rarely HAPA; direct rupture into major vessels and pericardium; and biliovascular fistula. These vascular complications can increase morbidity and may cause mortality among affected patients. Mortality is usually associated with rare but serious complications such as septic shock, pulmonary thromboembolism, and cardiac tamponade. Suspicion of vascular complications should be high if patients with LA show persistent, worsening, or new symptoms, despite receiving the recommended antibiotic therapy. Hemodynamically unstable patients might need immediate imaging to rule out life-threatening complications. Vascular problems may not show up on traditional ultrasound imaging, necessitating abdominal CT or MRI with angiography. The majority of vascular complications resolve with antibiotics and drainage of LA. Drainage is particularly necessary in large LAs, which are more likely to cause vascular complications. Abdominal ultrasonography is generally used to guide percutaneous drainage. Serial ultrasound examinations can be useful in monitoring therapeutic responses, besides clinical signs. The requirement for additional treatment will depend on the nature, severity, and course of the vascular complication. Thrombotic complications appear to resolve with treatment of LA alone, and anticoagulation is not necessary. Nonetheless, a small proportion of PVT patients, especially those diagnosed early in life, may develop chronic portal hypertension. Thus, individualized treatment and vigilant monitoring are required to ensure favorable patient outcomes. Additional research is necessary to shed more light on the risk factors and natural history of vascular complications, the appropriate timing and indication of intervention, and ways to prevent such complications.

FOOTNOTES

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SYSTEMATIC REVIEWS

Blastocystis hominis as a cause of chronic diarrhea in low-resource settings: A systematic review

Stephen Amoak, Jonathan Soldera

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Abstract

BACKGROUND

Blastocystis hominis (*B. hominis*), an anaerobic unicellular protist parasite, is known for its diverse clinical manifestations upon infecting the human gastrointestinal tract. Although globally distributed, it is particularly prevalent in developing nations. Examining the symptoms and treatment outcomes of *B. hominis* infection in low-resource settings holds immense significance, providing healthcare practitioners with valuable insights to enhance patient care.

AIM

To synthesize existing evidence on the symptomatology and treatment outcomes of *B. hominis* infection in low-resource settings.

METHODS

Following the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines, a systematic review was conducted. The search spanned electronic databases including PubMed, Scopus, and Google Scholar. After a comprehensive screening process, a thorough examination of the papers, adhering to inclusion and exclusion criteria, and data extraction from eligible studies was conducted. The findings underwent summarization through simple descriptive analysis.

RESULTS

The search yielded 1200 papers, with 17 meeting inclusion criteria. Chronic diarrhea due to *B. hominis* infection was reported in only two studies, while abdominal pain, diarrhea, flatulence, constipation, and nausea/vomiting emerged as the most commonly documented symptoms. Recovery rates after one week of treatment ranged from 71.8% to 100%, and after two weeks, from 60% to 100%.

CONCLUSION

In low-resource settings, chronic diarrhea resulting from *B. hominis* infection is infrequent. Common symptoms include abdominal pain, diarrhea, flatulence, constipation, and nausea/vomiting. Post-treatment, clinical outcomes are notably favorable, supporting the recommendation for treatment. Metronidazole is advocated as the first-line agent, with consideration for switching to a second-line option in cases of treatment failure or poor response.

Key Words: *Blastocystis* infections; Gastrointestinal diseases; Treatment outcome; Developing countries; Metronidazole/therapeutic use

Core Tip: This systematic review highlights the symptomatology and treatment outcomes of *Blastocystis hominis (B. hominis)* infection in low-resource settings. Notably, chronic diarrhea due to *B. hominis* is rare in these contexts. Abdominal pain, diarrhea, flatulence, constipation, and nausea/vomiting are the predominant symptoms reported. Post-treatment recovery rates are promising, ranging from 60% to 100% after two weeks of treatment. Metronidazole is recommended as the initial treatment, with consideration for alternative options if needed. These findings provide valuable insights for healthcare practitioners managing B. hominis infections in resource-limited settings.

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INTRODUCTION

Blastocystis spp. stand as anaerobic unicellular protist parasites categorized within the protozoan class *Blastocystea*. A part of the diverse and intricate stramenopiles group, they lack flagella and have the propensity to infect humans and various animals, establishing themselves as the most prevalent protozoa affecting the human gastrointestinal tract[1-3]. Recognized as the sole organism in this group causing human infections, *Blastocystis hominis* (*B. hominis*) is a significant focus of research and clinical attention[2-5].

The genetic diversity of *Blastocystis spp.* is evident through the polymorphic regions of its small subunit ribosomal ribonucleic acid gene (the small subunit ribosomal deoxyribonucleic acid), revealing at least 17 subtypes (ST1–ST17). While some subtypes are exclusive to humans, others are present in various hosts. Among the nine human subtypes (ST1–ST9), ST3 emerges as the most prevalent, followed by ST1, ST2, and ST4[6-10].

Global distribution characterizes *Blastocystis spp.*, affecting over 1 billion people worldwide, with higher prevalence in developing countries, ranging from 22.1% to 100.0%[5,11-16]. Various socio-economic, demographic, and epidemiological factors contribute to the higher prevalence observed in these regions[11,13-15,17]. Despite some studies confirming its pathogenicity in humans, there is inconclusive and controversial evidence, possibly due to *Blastocystis spp.*'s association with normal gut microbiota while being capable of causing opportunistic infections in immunocompromised patients[3,4,18-21].

The protist primarily colonizes the colon and cecum, showcasing a diverse clinical presentation[4,15]. In addition to common symptoms like diarrhea, constipation, flatulence, and abdominal pain, it can manifest extraintestinal clinical symptoms, including anorexia, urticaria, hypersalivation, fatigue, and anal pruritus. While fever is uncommon, associations with conditions such as irritable bowel syndrome (IBS) and chronic diarrhea are noted[4,5].

Morphologically, B. hominis exists in four distinct forms (cyst, ameboid, granular, and vacuolar) with the cyst form exhibiting a high resistance to chlorination and the ability to endure low gastric pH. The infection initiates with cyst ingestion, followed by excystation in the colon, leading to vacuolar forms. These vacuolar forms undergo binary fission, resulting in ameboid or granular forms. Ultimately, encystation may occur in the large intestine, leading to cyst shedding in stool[2]. The life cycle of *Blastocystis spp.* is not fully understood, but it is postulated that the cyst form is the infectious stage, while the vacuolar form is predominantly found in human stool specimens, with replication likely occurring *via* binary fission. Other morphologic forms, such as ameboid and granular forms, have been observed, though their biological roles require further investigation[22].

Diagnosis relies on detecting these characteristic forms in stool samples, with *B. hominis* being the most prevalent eukaryote in human stool samples[3]. Xenic culture and quantitative polymerase chain reaction assays are established diagnostic methods, especially when the infective cyst form is present, as direct smear detection can be challenging[2,5]. Currently, SSU-rDNA genotyping stands as the ultimate and preferred diagnostic technique in the literature and in clinical practice[23,24].

For the pharmacologic treatment of blastocystosis (*i.e.*, *B. hominis* infection), metronidazole is the reported drug of choice[20]. Second-line pharmacologic agents which may be considered include cotrimoxazole (trimethoprim/sulfamethoxazole), iodoquinol, tinidazole, ornidazole, paromomycin, nitazoxanide, chloroquine, pentamidine, emetine, furazolidone, and iodochlorhydroxyquin[20].

Gaining insights into the symptoms and treatment outcomes of *B. hominis* is crucial, particularly in resource-constrained settings. A systematic synthesis of existing literature and evidence can unearth patterns, treatment efficacy, and potential knowledge gaps. This study aims to present a comprehensive overview of *B. hominis* infection, encompassing its clinical manifestations and the efficacy of diverse treatment approaches in low-resource areas.

The research contributes valuable insights into the clinical presentation of *B. hominis* infection, enhancing our understanding of its symptomatology. Moreover, by scrutinizing the effectiveness of different treatment strategies in resource-limited settings, the review serves as a valuable resource for healthcare practitioners in such environments. This contribution aids in optimizing and enhancing patient care and management concerning *B. hominis* infection.

The principal aim of this research was to explore the symptomatology and treatment outcomes associated with *B. hominis* infection, particularly in low-resource settings (*i.e.*, developing countries).

MATERIALS AND METHODS

Study design

The study followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines[25]. The goal was to evaluate evidence from studies on the symptomatology of individuals infected with B. hominis in low-resource settings, examining the treatments administered and the clinical responses observed.

Eligibility criteria

The systematic review exclusively incorporated peer-reviewed studies published in English, with no constraints on study designs. Excluded from consideration were preclinical studies, reviews, conference abstracts, editor's notes, commentaries, and unpublished works. For eligibility and inclusion, studies had to align with the Population, Intervention, Comparison, and Outcome criteria, which encompassed the following: (1) Population: Patients residing in low-resource settings (*i.e.*, developing countries) diagnosed with *B. hominis* infection before initiating treatment; (2) Intervention: Various antimicrobial and medical treatments; (3) Comparison: The same patients in low-resource settings with *B. hominis* infection but assessed after treatment; and (4) Outcome: Evaluation of response rates and symptom amelioration following treatment.

Information sources and search strategy

A comprehensive literature search was conducted in August 2023 on the electronic databases PubMed (Medline), Scopus, and Google Scholar using the search term ["blastocystis" (All Fields) OR "blastocystosis" (All Fields) OR "b hominis" (All Fields)] AND ["treatment" (All Fields) OR "diagnosis" (All Fields) OR "epidemiology" (All Fields)] AND [humans (Filter)]. No publication date or study design limitations (other than review papers) were applied, but the language of publication was restricted to English.

Selection process

The identified studies from databases underwent an initial screening based on titles, abstracts, and keywords. Both authors conducted the screening and data collection independently, ensuring a thorough and unbiased selection process. Subsequently, full-text retrieval and comprehensive screening were conducted in accordance with the eligibility criteria, leading to the exclusion of studies that did not meet the specified criteria. The detailed process of study selection is delineated in Figure 1, employing the PRISMA 2020 flow diagram for new systematic reviews, encompassing searches of databases and registers exclusively[25,26].

Data extraction and synthesis

Comprehensive information, including authorship, publication year, study location, study design, population demographics, clinical manifestations, treatment modalities, and treatment outcomes, was systematically extracted from all incorporated studies. Both authors were involved in the data extraction process, which encompassed three primary variables: The documented clinical symptoms reported by individuals infected with B. hominis, particularly emphasizing chronic diarrhea; the specific treatments administered to patients; and the treatment response observed at one week, two weeks, and up to four weeks post-treatment. Response to treatment was categorized into fully recovered, improved but not fully recovered, or unchanged, and the percentages at each specified time frame were recorded.

RESULTS

Search results, study selection and study characteristics

A total of 1200 records were found upon applying the search term across three online databases, namely PubMed, Scopus, and Google Scholar. Preceding the screening process, eight duplicates were identified and promptly excluded. An additional 59 papers were excluded due to their classification as review papers, while 12 records, comprising books, book sections, or conference papers, were also excluded.

Subsequent to this initial culling, the remaining 1121 studies underwent thorough scrutiny based on title, abstract, and keywords, aligning with the predetermined inclusion criteria. This meticulous screening led to the removal of 1058

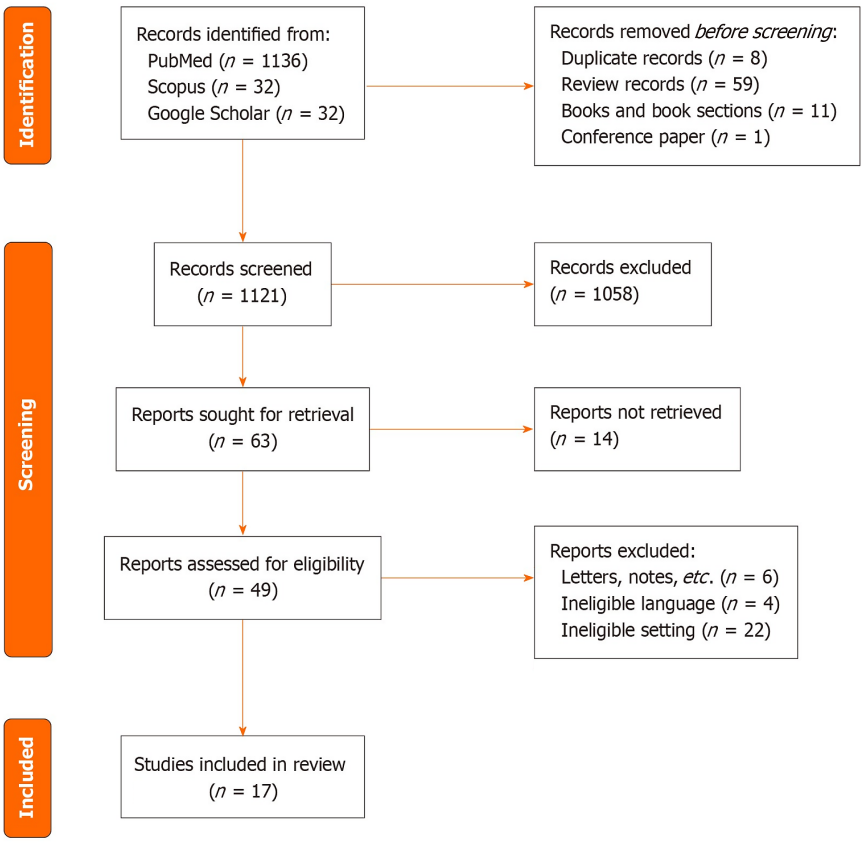

Figure 1 PRISMA flow diagram of selected studies.

papers. In the ensuing phase, 63 papers were earmarked for retrieval; however, 14 proved unattainable. Factors contributing to the unavailability of these 14 papers ranged from their antiquity, non-English language, to unresponsiveness from corresponding authors despite requests for full texts.

Ultimately, 49 full texts were successfully retrieved and subjected to a meticulous screening process, resulting in the exclusion of 32 papers. The rationale for removing these 32 papers rested on their classification as letters, comments, notes, or editorials, language disparities, or their origin from high-resource settings (*i.e.*, developed countries). The data extracted from the final selection of 17 studies were then analyzed to identify patterns, derive conclusive results, and form the basis for the study's conclusions. Figure 1 provides a PRISMA flow diagram illustrating the systematic selection of studies (Figure 1).

The 17 studies incorporated into this analysis were disseminated across peer-reviewed journals spanning the time frame from 1987 to 2020. These reports emanated from diverse geographical locations, representing four continents: 11 studies originated in Asia, three in Africa, two in North America, and one in Europe. A detailed breakdown by country reveals that five studies were conducted in Turkey[27-31], two in Egypt[32,33], and one each in Bosnia and Herzegovina [34], China[35], India[4], Iran[36], Iraq[37], Jamaica[38], Malaysia[39], Mexico[40], Morocco[41], and Saudi Arabia[42].

In entirety, there was a cumulative total of eight case reports sourced from six studies[4,27,34,38,39,41], two randomized controlled trials[28,33], one non-randomized trial[31], and one case-control prospective study[32]. The remaining seven studies were either retrospective[40] or prospective[29,30,35-37,42]. The total number of patients included in the review is 949. The reported sex distribution encompassed 494 males and 455 females. Table 1 comprehensively outlines the characteristics of the 17 studies incorporated in the analysis.

Results of synthesis

Chronic diarrhea in *B. hominis* infection: In terms of clinical presentation, chronic diarrhea was present in two studies [34,35] while data remain inconclusive for the study by Dinleyici *et al*[28]. In this particular study, a randomized single-blinded clinical trial, participants were required to exhibit symptoms for at least two weeks to qualify for inclusion.

In the case report conducted by Rajič *et al*[34], a previously healthy 49-year-old male with no underlying medical conditions developed angioedema, urticaria, and inconsistent stool with a 'mushy' appearance lasting a month. Unresponsive to a combination of a restrictive diet and loratadine, further investigations led to the diagnosis of *B. hominis* infection and Hashimoto's thyroiditis.

The study conducted by Tai *et al*[35] focused on six patients (equally divided between males and females and all aged 30–51 years) experiencing symptoms, such as diarrhea, persisting for durations ranging from eight to 26 months. Notably, all these patients were individuals with ulcerative colitis, showing resistance to standard treatments for the condition. Their stool examinations yielded positive results for *B. hominis* with no evidence of other pathogens.

Table 1 Characteristics of systematically reviewed studies

Ref.	Study design	Country	Population characteristics	Chronic diarrhea	Other symptoms	Treatment	Outcome
Andiran *et al* [27]	Case reports	Turkey	12-year male11-year male	Absent	Abdominal pain, anorexia, diarrhea, fever, Abdominal pain, diarrhea, fever, nausea, vomiting	MET and TMP/SMX (duration unknown) MET and TMP/SMX (duration unknown)	FR (time unknown) FR (time unknown)
Bhat Yellanthoor *et al*[40]	Case report	India	13-year male	Absent	Abdominal pain, bloody diarrhea, chills, diarrhea, fever, headache, rigors, vomiting	MET (duration unknown)	FR at 2 weeks
Dinleyici *et al* [28]	RCT	Turkey	48 children with symptoms ≥ 2 weeks; randomized into three treatment groups: A (11 males; 7 females); B (8 males; 7 females); C (7 males; 8 females)	Unknown	Abdominal pain (31 patients), anorexia (6 patients), diarrhea (22 patients), flatulence, nausea/vomiting (8 patients)	A: Lyophilized *Saccharomyces boulardii* for 10 days (n = 18); B: MET for 10 days (n = 15); C: None (n = 15); MET after 2 weeks (n = 9)	77.7% (14/18) FR at 2 weeks; 94.4% (17/18) FR at 4 weeks; 66.6% (10/15) FR at 2 weeks; 73.3% (11/15) FR at 4 weeks; [72.7% (24/33) FR at 2 weeks (total treated); 84.4% (28/33) FR at 4 weeks (total treated)]; 40% (6/15) FR at 2 weeks
Fréalle *et al*[41]	Case report	Morocco	9-year female	Absent	Abdominal pain, anorexia, diarrhea, fever, vomiting, weakness (acute appendicitis)	Appendectomy, TIN, CEF, GEN for 10 days	FR at 2 weeks
Guirges and Al-Waili *et al* [37]	Prospective	Iraq	103 patients (54 males, 49 females) aged 8–65 years	Absent	Abdominal pain, diarrhea, flatulence	MET for 7 days	71.8% (74/103) FR at 1 week; 71.8% (74/103) FR at 4 weeks; no data for 29 patients
Hameed *et al* [32]	Case control prospective	Egypt	104 participants (54 cases aged 3–59 years; 50 controls aged 7–65 years); 20 symptomatic cases followed up	Absent	Abdominal pain, constipation, diarrhea, fatigue, fever, flatulence, vomiting, urticaria	MET for 5–10 days (n = 20)	60% (12/20) FR at 2 weeks; 100% (20/20) FR at 4 weeks
Kaya *et al*[29]	Prospective	Turkey	52 patients (22 males; 30 females) aged 3–61 years; 41 followed up	Absent	Abdominal distention, abdominal pain, constipation, diarrhea, perianal pruritus, urticaria, weight loss	MET for 2 weeks	92.3% (36/39) FR at 2 weeks for intestinal symptoms; 50% (1/2) FR at 2 weeks for extraintestinal symptoms except weight loss; 0% (0/1) FR at 2 weeks for weight loss
Lee *et al*[38]	Case report	Jamaica	29-year female	Absent	Abdominal pain, arthralgia, bloody diarrhea, diarrhea, fever, joint swelling, morning joint stiffness, vomiting	MET for 5–7 days	FR at 1 week
Moghaddam *et al*[36]	Prospective	Iran	104 patients (60 males; 44 females) aged 52 ± 16 years	Absent	Abdominal pain (102 patients), constipation (19 patients), diarrhea (72 patients), fever (13 patients), flatulence (27 patients)	MET and TMP/SMX for 10 days	73.6% (76/104) FR at 2 weeks; 18.9% (19/104) PR at 2 weeks; 1.9% (2/104) NR at 2 weeks
Ok *et al*[30]	Prospective	Turkey	53 patients (38 children aged 5–14 years; 15 adults aged 17–66 years)	Absent	Abdominal pain (52 patients), constipation (10 patients), diarrhea (37 patients), fever (7 patients), flatulence (14 patients)	TMP/SMX for 7 days	73.6% (39/53) FR at 1 week; 18.9% (10/53) PR at 1 week; 7.5% (4/53) NR at 1 week
Qadri *et al*[42]	Prospective	Saudi Arabia	239 patients (43 followed up after treatment)	Absent	Abdominal pain (210 patients), alternating diarrhea and constipation (35 patients), anorexia (13 patients), constipation (77 patients patients), depression (8	MET for 7–10 days	No data for up to 4 weeks

					patients), diarrhea (56 patients), fatigue (25 patients), flatulence (4 patients), food intolerance (8), headache (9 patients), nausea (9 patients), vomiting (30 patients)		
Rajamanikam *et al*[39]	Case reports	Malaysia	13-year male30-year male	Absent	Abdominal pain, weight loss Chronic flatulence, discomfort, exhaustion	MET for 10 days MET for 10 days	Worse at 2 weeks
Rajič *et al*[34]	Case report	Bosnia and Herzegovina	49-year male	Present	Chronic urticaria, angioedema	MET for 14 days	FR at 2 weeks
Rossignol *et al* [33]	RCT	Egypt	100 patients (37 males; 47 females) aged 2–43 years randomized into two treatment groups of 50 each	Absent	Abdominal pain (78 patients), anorexia (4 patients), bloody stool (6 patients), diarrhea, fever (12 patients), flatulence (7 patients), mucoid stool (12 patients), nausea (7 patients), vomiting (5 patients)	NIT for 3 days (n = 42), None (n = 42)	86% (36/42) FR at 1 week, 38% (16/42) FR at 1 week
Tai *et al*[35]	Prospective	China	6 patients (3 males; 3 females) with refractory ulcerative colitis aged 30–51 years	Present	Bloody stool, purulent stool	MET for 10–14 days	100% (6/6) PR at 2 weeks
Taşova *et al*[31]	Non-randomized trial	Turkey	206 adults with hematological malignancy (118 males; 88 females; 23 studied)200 adults without hematological malignancy (110 males; 90 females; 2 studied)	Absent	Abdominal pain, bloating, diarrhea, flatulence, nausea/vomiting	MET for 10 days (n = 23), No data	100% FR at 2 weeks, No data
Toro Monjaraz *et al*[40]	Retrospective	Mexico	138 patients (58 males; 80 females)	Absent	Functional abdominal pain	MET (36), ALB (1), MEB/TIN (34), NIT (9), RIF (1), SEC (18) or TMP/SMX (1) 37 not treated	68.3% (69/101) FR (time unknown). 35.1% (13/37) FR (time unknown)

ALB: Albendazole; CEF: Ceftriaxone; FR: Full recovery; GEN: Gentamicin; MEB: Mebendazole; MET: Metronidazole; NIT: Nitazoxanide; NR: No recovery; PR: Partial recovery; RCT: Randomized controlled trial; RIF: Rifaximin; SEC: Secnidazole; TIN: Tinidazole; TMP/SMX: Trimethoprim/sulfamethoxazole.

Other symptoms of *B. hominis* infection: In addition to chronic diarrhea, the included studies reported an extensive array of symptoms, exceeding 25, attributed to or associated with *B. hominis* infection. The most frequently documented symptoms, in descending order, included abdominal pain, diarrhea, flatulence, constipation, and nausea/vomiting. In contrast, less common symptoms encompassed urticaria, arthralgia, joint stiffness, joint swelling, angioedema, depression, abdominal distension, headache, weight loss and peri-anal pruritus.

Beyond clinical symptoms, *B. hominis* infection demonstrated a capacity to mimic, cause, or contribute to other diagnoses or clinical syndromes. For instance, in two studies, the infection manifested as acute abdomen, particularly in the form of acute appendicitis[27,41]. Additionally, it was linked to urticaria, angioedema, and Hashimoto's thyroiditis, as reported by Rajič *et al*[34]. In another study, it was associated with seronegative polyarthritis[38].

Treatment outcomes

In all studies, patients received some form of treatment, with the exception of two studies where no treatments were provided to certain patients or groups[28,33]. The reported treatment regimens were diverse, encompassing the use of single or multiple antimicrobial agents, probiotic agents, or surgical intervention. These treatment modalities included metronidazole, trimethoprim/sulfamethoxazole, tinidazole, ceftriaxone, gentamicin, nitazoxanide, albendazole,

mebendazole, rifaximin, secnidazole, lyophilized *Saccharomyces boulardii*, and appendectomy.

The reported duration of treatment generally ranged from one to two weeks[28–42]. However, the treatment duration was unknown in two studies[4,27].

Metronidazole alone was reported as a treatment modality in twelve studies[4,28,29,31,32,34,35,37-40,42], while in two studies, it was administered in combination with trimethoprim/sulfamethoxazole[27,36]. Trimethoprim/sulfamethoxazole was employed as a sole treatment agent in two studies[30,40] and nitazoxanide alone was reported in two studies [33,40]. A single study[40] detailed the use of albendazole, secnidazole, or rifaximin alone. Only one study[28] reported lyophilized *Saccharomyces boulardii* as a treatment modality. Conversely, Fréalle *et al*[41] utilized a combination of appendectomy, tinidazole, ceftriaxone, and gentamicin in treating a patient.

All studies included in the analysis documented some degree of symptomatic improvement in patients, regardless of whether they received treatment or not. However, treated patients consistently exhibited higher and more favorable response rates compared to their untreated counterparts.

In studies providing data, the full recovery rate at one week ranged from 71.8% to 100% among treated patients[37,38], whereas untreated patients had a recovery rate of 38%[33]. Regarding partial recovery at one week, treated patients showed a rate of 18.9%[30], with no available data for untreated individuals. Moreover, 7.5% of treated patients experienced no change in symptoms after one week[30].

The two-week response rate for full recovery ranged from 60% to 100% among treated patients[4,31,32,41], whereas untreated patients exhibited a recovery rate of 40%[28]. Partial recovery rates at two weeks varied between 18.9% and 100%[35,36]. In contrast, two cases reported by Rajamanikam *et al*[39] did not show improvement and instead worsened clinically despite receiving treatment for two weeks. Additionally, Moghaddam *et al*[36] reported a non-response rate of 1.9% following a two-week treatment. No data were reported for untreated patients regarding partial or non-response rates at two weeks.

At the four-week mark, treated patients exhibited a full recovery rate ranging from a minimum of 71.8%[37] to a maximum of 100%[32]. Unfortunately, no data were reported for untreated patients, and there is an absence of information on partial recovery and non-response rates regardless of the treatment provision.

Recovery rates were also documented without specific timelines. For instance, Andiran *et al*[27] reported a 100% full recovery rate following treatment in two case reports, but the duration of recovery was unspecified. In Toro Monjaraz *et al*'s study[40], this figure decreased to 68.3%, with no documented timeframe for recovery, mirroring the previous study's lack of temporal details.

In cases where *B. hominis* infection was associated with other diagnoses or clinical syndromes, treatment often led to the resolution or improvement of these conditions. For instance, Rajič *et al*[34] reported that treatment for B. hominis resulted in the complete resolution of chronic urticaria, angioedema, and Hashimoto's thyroiditis. Similarly, Lee *et al*[38] found that B. hominis treatment led to the disappearance of seronegative arthritis, with no recurrence observed up to four months of follow-up. Previous studies have highlighted a strong association between B. hominis infection and conditions such as inflammatory bowel disease (IBD), IBS, and other intestinal disorders. This association poses significant health risks and adversely impacts the quality of life of affected patients, underscoring the public health concern it represents in China[43].

DISCUSSION

Chronic diarrhea in B. hominis infection

Available epidemiological data demonstrates that, *B. hominis* exhibits significant prevalence in tropical and subtropical settings, notably in developing countries where inadequate sanitary and hygienic conditions lead to the consumption of contaminated food or water[44]. Extensive studies have consistently associated *B. hominis* infection with chronic diarrhea, as highlighted by the work of Graczyk *et al*[45] and more recently by Jha *et al*[46]. Notably, Jha *et al*[46] reported a substantial *B. hominis* infection prevalence of 30% among patients experiencing chronic diarrhea, contrasting with an overall prevalence of 1.6% among the general study participants. In the context of low-resource settings, the synthesis from this review affirms that *B. hominis* infection presenting as chronic diarrhea is infrequent in such environments. Furthermore, the presence of chronic diarrhea often signals the likelihood of comorbidities. Among the most frequently reported comorbidities in these instances are the chronic digestive disorders, namely, IBS and IBD[11,17,46].

Per the available evidence, there is no doubt that there exists a demonstrable relationship between *B. hominis* and IBS. However, the exact nature of this relationship is elusive, a mystery and is the subject of much debate with no definitive conclusions. The question remains as to whether *B. hominis* is causally related to IBS, is only associated with it, or simply mimics the condition[47-53].

In a case study by Hahm[47], a 32-year-old male had a five-year history of bloating (his predominate symptom), chronic diarrhea, and rectal urgency. This was associated with abdominal pain and in addition, bowel motion was not a relieving factor for the bloating sensation. He reported negative symptoms for blood or mucus in his stool as well as weight loss. Having been previously diagnosed with IBS (diarrhea predominant) by a gastroenterologist, he received a probiotic and modified diet as his treatment regimen. Regardless, these interventions failed to ameliorate his condition. Laboratory studies of his stool were positive for *B. hominis* and on that basis, treatment with metronidazole was commenced. This therapy did lead to a complete alleviation of his symptoms after 14 days. Accordingly, the author concluded that *B. hominis* mimics IBS, further arguing that patients presenting with IBS symptoms should undergo early testing for *B. hominis* as this may be beneficial[47]. This proposition is buttressed further by Ragavan *et al*[50] who recommend colonoscopy with PCR examination of stool aspirates, in IBS patients suspected to have *B. hominis* infection

but who otherwise report a negative stool exam.

In a review article by Lepczyńska *et al*[48], it is argued that the concept of *B. hominis* being etiologically linked with IBS is inconclusive owing to the controversial nature of the organism as a human pathogen. On one hand, the authors affirm that the non-specific symptoms of blastocystosis are very much IBS-like and since enteric inflammation has been postulated to be one of the mechanisms in the pathogenesis of IBS, infection with *B. hominis* may be a contributory factor. Additional evidence in support of this causal posture is the fact that the protozoan is able to colonize the bowel by producing a proteolytic enzyme (cysteine protease) that breaks up IgA antibody, causing gut inflammation and a disturbance of the intestinal barrier function. However, it appears that it is some subtypes of *B. hominis* (ST4 and ST7) that possess this pathogenic ability and are able to cause disease in some but not all patients.

The notion that there is inconclusive evidence on the association between *B. hominis* infection and IBS is further articulated in an epidemiological study by Salvador *et al*[51]. In their study, 36 asymptomatic patients were compared with IBS patients of an equal number and the prevalence of blastocystosis was determined in each group. Interestingly, the healthy controls reported a higher prevalence than their IBS counterparts but this finding was not statistically significant. Accordingly, the authors concluded that further studies are required to provide clarity on the relationship.

In summary, piecing together the available evidence lends credence to the conclusion that there is indeed a growing suspicion among authors that *Blastocystis spp*. plays a role in the pathogenesis of IBS[47-53]. This suspicion gains support from numerous studies indicating a higher incidence of the organism in patients with IBS compared to healthy individuals[49]. While these studies do not definitively establish *B. hominis* as a causative agent for IBS or IBD, they underscore its contributory role in the pathogenesis of these conditions.

The evidence derived from the present synthesis aligns with this pattern, as both of the included studies reporting chronic diarrhea also identified comorbidities in affected patients, specifically Hashimoto's thyroiditis[43] and ulcerative colitis[35]. While the third study, a randomized single-blinded clinical trial conducted by Dinleyici *et al*[28] among children at the Eskisehir Osmangazi University Faculty of Medicine Hospital in Turkey, may have involved participants with chronic diarrhea, the explicit duration of their symptoms, particularly whether lasting for at least four weeks, remains unknown. However, in contrast to the previous two studies, these children reported no comorbidities. Remarkably, the study's exclusion criteria encompassed hospitalization for any reason, medication use in the preceding month, presence of a comorbidity, and a positive stool result for any other infective organism besides *B. hominis*. Consequently, it is plausible that in low-resource settings, *B. hominis* is not only associated with chronic diarrhea but may indeed be a causative factor, even if such occurrences are infrequent.

Other symptoms of B. hominis infection

The additional symptoms outlined in this comprehensive review align with those documented in prior studies, supporting the notion that infection with the protist can manifest clinically in diverse ways[15,54]. Given that the gastrointestinal tract, particularly the colon and cecum, serves as the typical habitat for the organism, gastrointestinal symptoms like abdominal pain, diarrhea, flatulence, constipation, and nausea/vomiting are notably prevalent and expected[15,54]. Intriguingly, in this investigation, abdominal pain surpassed diarrhea as the most frequently reported symptom, a departure from the observations of Roberts *et al*[54] and Salvador *et al*[55], where diarrhea claimed the top spot in frequency. This divergence could potentially reflect the influence of different settings, as the mentioned studies were conducted in high-resource localities. The outcomes of this study imply that, when evaluating patients with the specified symptoms, suspicion of *B. hominis* infection should be considered and included in the differential diagnoses, particularly in cases involving the ingestion of contaminated food or water, or when stool examination yields negative results for other common pathogens such as *Giardia lamblia*, *Cryptosporidium sp*., *Dientamoeba fragilis*, *Entamoeba sp*., *Cyclospora sp*., and *Cystoisospora sp*.

Despite the aforementioned considerations, the study also revealed that blastocystosis might present atypically, manifesting in less common ways, including urticaria, angioedema, joint stiffness, and joint swelling. This atypical presentation can be attributed to the protist's potential dissemination to extraintestinal parts of the body, akin to other infections. In such instances, additional and localized symptoms may surface. Moreover, acting as a foreign entity, the organism may trigger an immunological response, resulting in cutaneous lesions such as urticaria and angioedema.

Treatment outcomes

Treatment for blastocystosis is typically initiated when patients exhibit chronic or persistent symptoms, have compromised immune systems, or present other pathogens in their stool examination[2,20]. While various antimicrobial agents have been reported in other studies for treating *B. hominis* infection, such as ornidazole, paromomycin, chloroquine, pentamidine, emetine, furazolidone, paromomycin, iodoquinol, and iodochlorhydroxyquin, these were not employed in the studies reviewed here.

Nevertheless, the evidence synthesized in this study aligns with other research, highlighting metronidazole as the most frequently utilized agent, solidifying its status as the primary antibiotic treatment choice[20,27,33,54]. The first comprehensive assessment of metronidazole's efficacy was carried out in a large-scale placebo-controlled trial by Nigro *et al*[56]. Conducted among immunocompetent patients with *B. hominis* as the sole intestinal parasite, the study showcased the drug's effectiveness in resolving diarrhea and inducing clinical remission. By implication, this trial substantiated the organism's capacity to trigger intestinal disease.

In terms of clinical outcomes, patients may spontaneously recover or witness symptom improvements even in the absence of formal treatment. This review unequivocally illustrates that within a week of treatment initiation, a minimum of approximately 70% of patients achieve full recovery, and by the end of a month, this rate escalates, approaching 100%. Clearly, treatment yields superior outcomes and proves highly favorable. However, the review also highlights instances of treatment failure, wherein patients exhibit no improvement, and some even experience exacerbated symptoms. The

potential cause of this variable drug susceptibility is attributed to drug resistance stemming from mutations, such as the ATP-binding cassette transporters identified in the ST7 genome[2,57].

As emphasized by Roberts *et al*[54], instances of treatment failure underscore the necessity for extensive antimicrobial testing, expanding the arsenal of treatment alternatives available for managing blastocystosis when treatment proves ineffective. Despite this challenge, second-line agents (trimethoprim/sulfamethoxazole, iodoquinol, tinidazole, ornidazole, paromomycin, nitazoxanide, chloroquine, pentamidine, emetine, furazolidone, and iodochlorhydroxyquin) can be employed in such cases to enhance treatment outcomes[2,20].

In low-resource settings, the occurrence of chronic diarrhea due to *B. hominis* infection is infrequent. Conversely, when chronic diarrhea is evident, the likelihood of an additional diagnosis being present or causative is higher. Consequently, it is imperative to conduct a comprehensive clinical assessment or investigation to identify other potential diagnoses or pathogens in such scenarios, such as IBS[58], IBD[59-63], celiac disease[64,65], other chronic or acute infections[66-69], neoplasm[70] and drug induced diarrhea[71-73].

More frequently, symptoms such as abdominal pain, diarrhea, flatulence, constipation, and nausea/vomiting may manifest following B. hominis infection. It is crucial to recognize that the protozoan's infection can exhibit atypical presentations, including urticaria, depression, arthralgia, joint stiffness, joint swelling, angioedema, and peri-anal pruritus. Additionally, *B. hominis* has been associated with acute appendicitis, as highlighted by a recent case report of a 9-year-old boy who developed appendicular peritonitis due to this pathogen[74]. Furthermore, instances of B. hominis being identified in peritoneal fluid, even in patients undergoing peritoneal dialysis, underline the protozoan's potential pathogenicity in non-intestinal sites[75,76]. Thus, B. hominis should be considered in these clinical scenarios, particularly when treatments for presumed and more conventional diagnoses yield minimal or no response.

Despite the generally favorable clinical outcomes observed in individuals infected with B. hominis, treatment markedly improves results, leading to a quicker recovery rate with antimicrobial or alternative therapies. Treatment also aids in resolving comorbidities triggered or worsened by B. hominis infection. Therefore, while patients with mild symptoms may recover spontaneously or due to resource limitations, it is advisable to treat those with moderate to severe symptoms to optimize clinical outcomes. Metronidazole is recommended as the initial treatment, with a switch to a second-line option in cases of treatment failure or inadequate response.

However, it should be noted that the study's reliance on a limited number of databases may have constrained the scope of the literature review, which is a limitation that should be considered when interpreting the results. Additionally, the lack of prospective registration of this review in PROSPERO is a limitation that may impact the transparency and reproducibility of the study's findings. Furthermore, the absence of a formal bias assessment tool in this review is a limitation that may affect the evaluation of the included studies' quality. Additionally, the inclusion of 6 case reports out of 17 articles highlights a limitation in the scope of evidence available, which may impact the generalizability of the findings.

CONCLUSION

Future research, including meta-analyses and randomized controlled trials, is needed to better understand treatment response rates for *B. hominis* and identify the most effective therapies, especially in low-resource settings. A key area for investigation is distinguishing B. hominis infection from IBS-D. As IBS-D is a common cause of chronic diarrhea, it's important to test for B. hominis in patients who do not respond to standard IBS-D treatments. Improved diagnostic clarity will help ensure more accurate treatment and better outcomes for patients with chronic diarrhea.

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FOOTNOTES

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SYSTEMATIC REVIEWS

Role of intestinal ultrasound in ulcerative colitis: A systematic review

Partha Pal, Mohammad Abdul Mateen, Kanapuram Pooja, Nandhakumar Rajadurai, Rajesh Gupta, Manu Tandan, Nageshwar Reddy Duvvuru

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Abstract

BACKGROUND

Intestinal ultrasound (IUS) is an emerging, non-invasive, and highly sensitive diagnostic tool in inflammatory bowel disease (IBD), including ulcerative colitis (UC). Despite its potential, its adoption in clinical practice is limited due to a lack of standardization and awareness.

AIM

To perform a comprehensive scoping review based on a systematic literature review on IUS in UC to inform current practice.

METHODS

Ninety-nine original articles about ultrasonography in UC were identified among 7608 citations searching PubMed and EMBASE databases for systematic review.

RESULTS

IUS can be useful as an initial diagnostic strategy in patients with suspected IBD/UC. In UC, IUS can predict endoscopic response, histologic healing, and steroid responsiveness in acute severe cases. IUS can predict response to biologics/small molecules (as early as 2 wk). IUS correlates well with ileo-colonoscopy, but IUS could miss rectal, jejunal, and upper GI lesions in suspected IBD and colon polyps or extra-intestinal manifestations in known IBD. IUS is useful in special situations (children, pregnancy, and postoperative Crohn's disease). Inter-observer agreement is acceptable and trained physicians have comparable diagnostic accuracy. Point-of-care ultrasound impacted management in 40%-60% of cases. Hand-held IUS has excellent agreement with conventional IUS.

CONCLUSION
IUS is a non-invasive, highly sensitive tool in the diagnosis and monitoring of UC, offering excellent patient satisfaction. Point-of-care ultrasound by IBD physicians can significantly impact clinical decision-making.

Key Words: Ulcerative colitis; Intestinal ultrasound; Inflammatory bowel disease; Diagnosis; Monitoring

Core Tip: Intestinal ultrasound (IUS) is an emerging non-invasive diagnostic tool for ulcerative colitis (UC) with high sensitivity. This scoping review demonstrates IUS's effectiveness in predicting endoscopic response, histologic healing, and steroid responsiveness in UC, as well as its role in early prediction of biologic response. While IUS may not detect all lesions, it shows excellent agreement with ileo-colonoscopy and is valuable in special situations like pregnancy and pediatric cases. Hand-held IUS matches conventional IUS in accuracy. Point-of-care IUS by inflammatory bowel disease physicians can significantly influence clinical decisions, underscoring its potential for broader clinical adoption.

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INTRODUCTION

Intestinal ultrasound (IUS) is emerging as a non-invasive, sensitive monitoring tool to assess inflammatory bowel disease (IBD) activity. Although IUS was first described more than two decades ago, it was not widely adopted, possibly due to a lack of proper training and concerns about accuracy compared to standard cross-sectional imaging or endoscopy. Current diagnostic methods, such as ileo-colonoscopy and magnetic resonance enterography (MRE), are effective but have limitations. Ileo-colonoscopy, while considered the gold standard for assessing mucosal inflammation, is invasive, costly, and not always well-tolerated by patients. MRE, though non-invasive and highly accurate, is expensive, time-consuming, and not universally accessible. These limitations underscore the need for a complementary diagnostic tool that is accurate, non-invasive, cost-effective, and widely accessible[1].

Recently, there has been renewed interest in gastroenterologist-led IUS. Patient satisfaction is excellent due to its non-invasive nature and point-of-care ultrasound (POCUS) with minimal waiting time. Over the last five years, there has been a surge in the literature investigating various aspects of IUS, ranging from validation of accuracy with endoscopy/cross-sectional imaging to its impact on managing IBD[2].

Current indications include suspected IBD, assessment of disease activity and complications (intestinal and extra-intestinal), monitoring therapeutic response, and prediction of clinical outcomes[2-4]. However, there is a need for more studies on several aspects of the evidence-based application of this tool, such as its use in a treat-to-target strategy. There is also a lack of validated scores for response or outcome prediction and a lack of age-specific cutoffs for the pediatric population. Despite current limitations and knowledge gaps, IUS can significantly impact clinical decision-making in IBD.

We aimed to present a comprehensive and updated review of IUS in ulcerative colitis (UC) by systematically analyzing the existing evidence, which is expanding like never before. The objective is to highlight the evidence behind IUS in UC to inform clinical decision-making.

MATERIALS AND METHODS

Search strategy

For the review, we searched PubMed and EMBASE with the following search criteria: ('intestinal ultrasound' OR 'bowel ultrasound' OR 'transabdominal ultrasound' OR 'ultrasonography') AND ('ibd' OR 'inflammatory bowel' OR 'colitis ulcerosa'/exp OR 'colitis ulcerosa' OR 'ulcerative colitis'/exp OR 'ulcerative colitis'). After excluding duplicates, we found 7608 records between 1986 and April 2024 (PP and KP performed the search individually). We screened all the titles and abstracts as well as the full text of selected articles. Finally, 99 original research articles on IUS were included for this scoping review excluding review articles/letters to the editor/editorials/pictorial surveys/case reports/ narrative reviews/systematic reviews/consensus/articles in a language other than English/translational research/articles not focused on the topic (Figure 1). We summarized the evidence under each subheading based on the review of the existing literature. In the areas where the literature was substantial, we represented it in a tabular form.

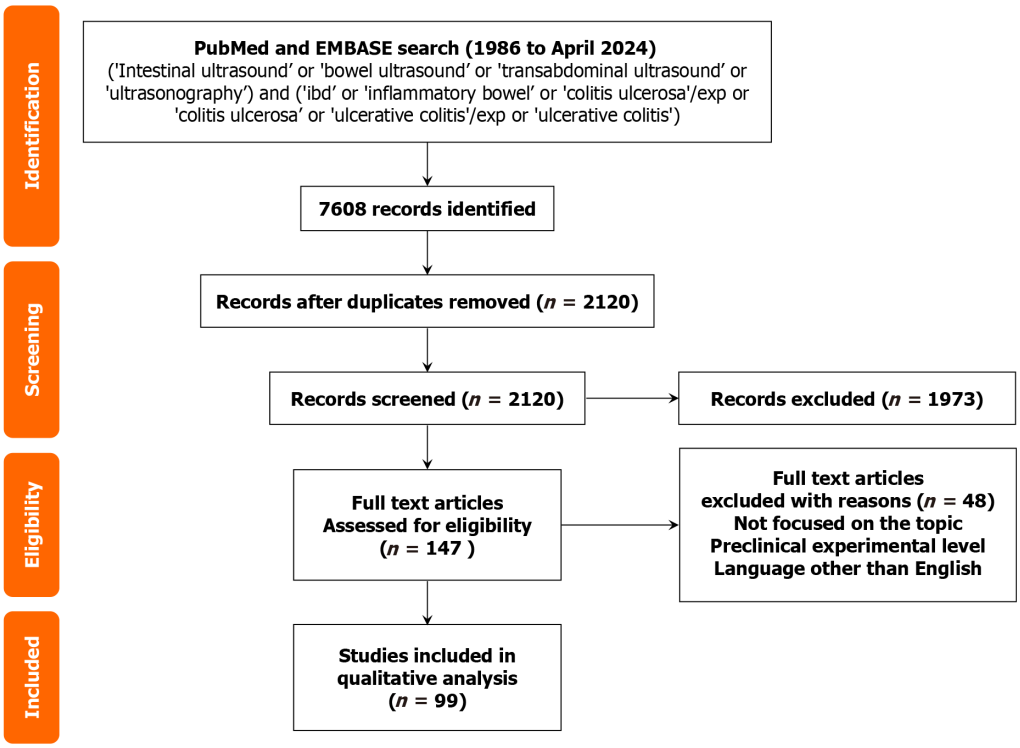

Figure 1 PRISMA diagram for systematic review.

RESULTS

IUS as a diagnostic strategy in suspected IBD/UC

IUS aids in IBD/UC diagnosis in those with low-risk GI symptoms by excluding irritable bowel syndrome. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of IUS in suspected IBD based on three prospective studies ranged between 55%-85%, 95%-100%, 92%-98%, and 58%-92%, respectively. However, there were wide variations in criteria for abnormal IUS findings [including cut-off for abnormal bowel wall thickness (BWT)], reference standard to the diagnosed IBD, age group studied, and frequency of ultrasound probes used to diagnose IBD (Table 1)[1,3,5,6]. Sensitivity was higher for the diagnosis of Crohn's disease (CD) (84%) than UC (38%-66%) [1,5]. Location-wise, sensitivity was higher for inflammatory ileal (92%-96%) and left colonic lesions (81%-87%) whereas it was low for duodenal/jejunal (29%-33%) and rectal lesions (14%-15%) (Table 1)[3,5]. Reduction in the BWT cut-off from ≥ 7 mm to ≥ 5 mm increases the sensitivity marginally with a reduction in specificity and PPV[1]. Among various IUS parameters, loss of stratification had the highest sensitivity (78.3%), whereas any of the three parameters (BWT, loss of stratification, and inflammatory fat) had an 82.6% sensitivity in a retrospective study of suspected pediatric IBD. The presence of all the three parameters had a 100% specificity and 100% PPV[7]. The presence of any of the three parameters had a 95.1% NPV (Table 1). A small study (n = 28) in suspected pediatric IBD showed that the sensitivity of IUS (55%) can be improved by magnetic resonance imaging (MRI) (sensitivity: 83%-87%)[8].

Utilization of IUS in those with low-risk GI symptoms from general practitioner referrals was shown to reduce colonoscopies and gastroenterology consults in a prospective study from Australia (Table 1)[9].

Role of IUS in differentiating UC from its mimics: It is not known whether IUS can help differentiate UC from its mimics. One of the initial retrospective studies concluded that high vascularity alone, without spectral waveform analysis, cannot differentiate between various inflammatory and neoplastic pathologies. Color Doppler sonography can only help to differentiate inflammatory lesions from small bowel ischemia. Vascularity was more pronounced in CD and cytomegalovirus colitis whereas a mild increase was noted in UC and diverticulitis[10]. However, contrast-enhanced ultrasound (CEUS) findings can help differentiate IBD from colon cancer: Disordered enhancement (94.7% cancer, 9.1% IBD), heterogeneous enhancement (78.9% cancer, 0% IBD), delayed enhancement (wash in time 14.7 ± 3.2 s cancer, 9.9 ± 3 s IBD), longer time to peak intensity (8.7 ± 2.9 cancer, 5.4 ± 2 IBD) (P < 0.001), and slow washout (in cancer)[11].

A small retrospective study from India (n = 76) used a two-step protocol to differentiate causes of chronic diarrhea with abdominal pain. Initially, lesions on IUS were divided based on shear wave elastography (SWE) and dispersion (SWD) to differentiate fibrotic (high SWE, normal SWD), inflammatory (normal SWE, high SWD), and mixed strictures (high SWE and SWD). Then CD (fat, fistula, vascularity), UC (inflammatory, thickened submucosa, preserved stratification, high SWD in submucosa), neoplastic etiology (BWT > 9 mm, SWE > 90 kPa), tuberculosis (nodes, fluid), infective ileocolitis (inflammatory or mixed), and diverticulitis could be differentiated based on involved bowel length, thickness, stratification, vascularity, fat, fluid, fistula, and lymph nodes[12].

IUS in UC

Assessing disease activity: Several IUS parameters have been used to assess disease activity[13,14]. Among them, the interclass correlation was perfect, substantial, moderate, and fair for BWT, Color Doppler signal (CDS) intensity, lymph node and mesenteric fat/loss of haustrations/bowel wall stratification as shown in an inter-observer agreement (IOA) study of six expert sonographers. Hence, it was concluded that BWT and CDS are reliable and can be incorporated in future UC scoring indexes[15]. Although there are several scoring systems available for assessing disease severity, we included those that are validated in original studies.

Milan criteria: In the developmental phase of Milan criteria (earlier Humanitus ultrasound criteria), BWT and CDS independently predicted colonoscopic activity on multivariate analysis (Table 2). Milan ultrasound criteria (MUC) [1.4 × BWT (mm) + 2 × CDS (CDS = 1 if present, 0 if absent)] was highly predictive of endoscopic activity [Mayo endoscopic score (MES) ≥ 2] (sensitivity: 71%, specificity: 100%, area under the curve (AUC): 0.891) with high IOA (kappa 0.86). The additional fecal calprotectin (FCP) increased sensitivity to 100%[16]. In an external validation study (n = 43), MUC > 6.2 had a 95% sensitivity and 94% specificity[17]. At more than 1 year follow-up, MUC > 6.2 could predict adverse disease outcomes (treatment escalation, steroid use, hospitalization, colectomy)[18]. MUC ≤ 6.2 at 12 wk (for UC patients on biologics) independently predicted endoscopic activity (MES ≤ 1) at 1 year (odds ratio [OR]: 5.8). A ≥ 2 reduction in MUC predicted MES = 0 (AUC: 0.816) (100% sensitivity, 62% specificity). MUC ≤ 4.3 was the most accurate for predicting MES = 0 (sensitivity 100%, specificity: 76%)[19].

In those with clinical remission, MUC > 6.2 predicted clinical relapse in a small retrospective study[20]. One step ahead, a small (n = 29), paired, cross-sectional study has shown that MUC > 6.2 along with elevated FCP ≥ 100 μg/g can accurately predict histologic activity in 88% of cases[4]. A higher cut-off of MUC > 7.7 was better in predicting colectomy (AUC: 0.83) risk than MES (AUC: 0.71)[21]. MUC calculated *via* a hand-held IUS machine has excellent agreement (kappa 0.86) and comparable accuracy (0.84) as compared to MUC calculated by conventional IUS (0.87)[22].

UC-IUS index: This index was developed based on a prospective study in which IUS and colonoscopy were done within 3 wk (60 patients, 207 colonic segments). UC-IUS index (scores 0-7) is based on BWT (scores 1, 2, and 3 for > 2 mm, > 3 mm, and > 4 mm, respectively), CDS intensity (present: Score 1, stretches: Score 2), lack of haustrations (score 1, predicting active disease), and fat wrapping (score 1, predicting severe disease). This scoring is based on the fact that BWT > 2.1 mm, > 3.2 mm, and > 3.9 mm can effectively differentiate between Mayo 0 and Mayo 1-3, Mayo 0-1 and Mayo 2-3, and Mayo 3 and others, respectively, with excellent accuracy (AUC > 0.9 for all) and sensitivity/specificity (all > 80%). The UC-IUS score showed a strong correlation with endoscopic scores, specifically the Mayo and UC Endoscopic Index of Severity (UCEIS) (Table 2) with substantial inter- and intra-rater agreement[23]. In the same study, a BWT > 2 mm and FCP > 200 μg/g resulted in a sensitivity of 76.9% and specificity of 93.3% for detecting endoscopically active disease[23].

Kyorin ultrasound criteria/submucosal index: Kyorin ultrasound criteria (KUC) can predict endoscopic activity without color Doppler. KUC is defined as BWT < 3.8 mm with submucosal index (SMI) (thickness of submucosa/entire bowel wall) < 50%. The PPV (95%) was higher than that of conventional criteria (BWT > 3 mm) to predict endoscopic improvement[24].

Monitoring therapeutic response and disease course in UC

The short-term, intermediate, and long-term goals of the management of UC are clinical response followed by normalization of biomarkers and finally mucosal healing with optional histologic healing. We found 13 studies (2 retrospectives, 1 *post-hoc* analysis of randomized trial, and 10 prospective studies) evaluating response to treatment in UC. Study designs vary from cross-sectional to follow-up periods of up to 1 year (Table 3).

One very early, small (n = 9 UC), retrospective study by Dubbins *et al*[25] did not show any significant changes in BWT for UC treated with conventional therapy at 2-4 mo as opposed to a significant reduction in CD (n = 19). However, Maconi *et al*[13] demonstrated that active UC treated with steroids resulted in a significant reduction in BWT in clinical responders, showing excellent correlation between IUS parameters and clinical, biochemical, and endoscopic measures. Further studies showed that early IUS response at 2-3 wk (2.5 mm reduction in BWT) for UC on conventional therapy and cytapheresis could predict treatment response (91% *vs* 40%) at 1 year with a lower probability of relapse (9% *vs* 47%)[26]. A small study (n = 7 UC) demonstrated significant changes in CEUS parameters, such as peak enhancement, and amplitude-dependent parameters with vedolizumab therapy at 14 wk, while no significant changes were observed in time-dependent parameters, such as time to peak[27].

A large, multi-center, German, prospective study (TRUST UC) has shown that 89% of patients with the clinical flare of UC had increased BWT in the descending/sigmoid colon which decreased significantly as early as 2 wk preceding clinical and biomarker response. Normalization of BWT at 12 wk had an excellent correlation with clinical response. This study supports the role of IUS as a noninvasive monitoring tool in IBD[28]. Subsequently, another prospective study including UC (n = 28) and CD (n = 89) from Romania showed that IUS parameters [BWT, CDS, and bowel wall stratification (BWS)] could predict immediate and subsequent treatment escalation over the next 6 mo[29].

A small (n = 31, 8 UC), retrospective study showed that a 16% improvement in BWT at 6 wk and 10% improvement at 14 wk predicted long-term treatment response at 46 wk in patients on biologics[30].

A more recent, prospective cross-sectional study showed that for UC patients on maintenance infliximab, lower trough levels were associated with IUS activity (higher CDS)[31]. A *post-hoc* analysis of prospective studies has shown that after 12 wk of treatment intensification, transmural healing (TH) was achieved in 45%-61% of UC cases and transmural response [(TR): ≥ 25% reduction or normalization of BWT)] in 76%[32].

Table 1 Summary of studies evaluating intestinal ultrasound for diagnosis of inflammatory bowel disease/ulcerative colitis and differentiating inflammatory bowel disease mimics

Ref.	Study type	Number of patients	Equipment	Criteria for abnormal findings	Reference	Sensitivity	Specificity	PPV	NPV
Hollerbach *et al*[5]	Prospective	227 suspected IBD patients	5 MHz curved array probe	BWT > 4 mm, target sign, lumen < 4 mm, ascites, abscess, reduced compressibility, conglomerate tumor (any 2 of the above)	Colonoscopy, entero-clysis, enema, CT scan, surgery	76% (84% CD, 66% UC) (10%-20% in jejunum, duodenum, rectum)	95%	98%	58%
Astegiano *et al*[1]	Prospective	313 (abdominal pain and altered bowel habits ≥ 3 mo)	7.5-10 MHz linear probe and 3.5 MHz convex probe	BWT ≥ 7 mm, BWT between 5-6 needs follow-up	Radiology and endoscopy	74% (84% CD, 38% UC)	98%	92%	92%
Chavannes *et al*[72]	Cross-sectional, single centre	33 children with suspected IBD (11 UC)	3-12 MHz linear probe and 3-10 MHz convex probe	BWT > 1.9 mm cut-off for inflamed bowel	Colonoscopy	64%	76%	-	-
Rossaint *et al*[3]	Prospective	487 suspected IBD patients	7.5 MHz linear, 3.5 MHz convex	BWT > 4 mm	Endoscopy, small bowel enteroclysis, CT	85% Rectum: 14% Duodenum/jejunum: 29%	95%	98%	75%
Dell'Era *et al*[7]	Retrospective	113 suspected pediatric IBD patients	3.5-5 MHz curvilinear probe, 4-8 MHz microconvex probe	BWT, BWS, lymph nodes, i-fat	Ileo-colonoscopy	BWS: 78.3% i-fat: 65.2%; BWT > 3: 69.6%. All 3: 56.5%. Any of 3: 82.6%	BWS: 93.3. i-fat: 92.2%; BWT > 3: 96.7%. All 3: 100%; Any of 3: 86.7%	BWS: 75% i-fat: 68.2%; BWT > 3: 84.2%; All 3: 100%. Any of 3: 61.3%	BWS: 94.4% i-fat: 91.2%; BWT > 3: 92.6%; All 3: 90%. Any of 3: 95.1%
Ziech *et al* [8]	Prospective	28 children with suspected IBD	Linear probe 5-12 MHz	BWT, BWS, lymph nodes, Doppler of mesenteric arteries	Ileo-colonoscopy and endoscopy	55% (improved with combination of MRI 83%-87%)	100%	-	-
White *et al* [9]	Prospective	37 patients with low-risk GI symptoms, FCP < 150 μg/g, CRP < 10 g/d	5-8 MHz curvilinear probe, 18 MHz linear probe	BWT > 3 mm, increased CDS, loss of BWS, inflammatory fat, lymph nodes	NA	-	-	-	-
Jeffrey *et al* [10]	Retrospective	32 patients with focal GI lesions, 20 controls	5 MHz linear array transducer	≥ 4 blood vessels measuring 3 mm or more over 5 cm segment/extending into mesentery	Surgery, biopsy, endoscopy	-	-	-	-
Zhang *et al* [11]	Retrospective	13 IBD, 38 colon cancer	Curvilinear probe 2-5 MHZ (for CEUS, MI 0.07-0.10, dynamic range 50 dB), linear probe 3-9 MHz, SonoVue contrast	Increased BWT, loss of BWS, "comb-teeth like" vessels on color Doppler, disordered enhancement, hetero-geneous enhancement	Histology for colon cancer, clinical/pathologic and endoscopic exams for IBD	Colon cancer BWS: 97.4%; Disordered enhancement: 94.7%. Heterogeneous enhancement: 78.9%	Colon cancer BWS: 69.2%; Disordered enhancement: 92.3%. Heterogeneous enhancement: 100%	-	-
Kapoor *et al* [12]	Retrospective, single centre	76 patients with chronic diarrhoea and abdominal	Convex probe: 3.5-8 MHz, linear probe: 8-14 MHz	Abnormal bowel wall stiffness (> 12 kPa) and abnormal inflammation (> 14 m/s/kHz); wall thickening (> 3	Contrast enhanced CT, endoscopic and surgical biopsy	100%	99%	-	-

	pain	and > 4 for small and large bowel), stratification, node, fluid, fat, and fistula

IBD: Inflammatory bowel disease; BWT: Bowel wall thickness; CD: Crohn's disease; UC: Ulcerative colitis; CT: Computed tomography; IBS: Irritable bowel syndrome; PPV: Positive predictive value; NPV: Negative predictive value.

Table 2 Studies evaluating scoring systems to assess disease activity in ulcerative colitis based on intestinal ultrasound

Ref.	Study type	Follow-up duration	IUS activity	Comparator	Number of patients	Results
Allocca *et al*[16]	Prospective	6 mo	BWT, CDS, BWS, lymph nodes	Colonoscopy	53 UC patients	BWT and CDS were independent predictors of colonoscopic activity; Humanitus ultrasound criteria: (1) BWT > 3 mm with CDS; and (2) BWT > 4.43 and absence of CDS. MUC > 6.2: Sensitivity 71%, specificity: 100%, AUC: 0.891. Addition of FCP increased sensitivity to 100%
Allocca *et al*[17]	Prospective	6 mo	BWT, CDS	Colonoscopy	43 UC patients	MUC score > 6.2 discriminated active UC (sensitivity 85%, specificity 94%, AUC 0.902); external validation study
Allocca *et al*[18]	Prospective	1.6 years (median)	MUC	-	98 UC patients	Milan ultrasound criteria > 6.2 at baseline was statistically significantly associated with adverse disease outcomes (treatment escalation, steroid use, hospitalization, and colectomy) (HR: 3.87)
Allocca *et al*[19]	Prospective	1 year	MUC	Colonoscopy	49 UC patients	MUC ≤ 6.2 at wk 12 is independent predictor of MES ≤ 1 at 1 year (OR: 5.8)
Maeda *et al*[20]	Retrospective	1 year	Milan criteria	Endoscopic Mayo score, fecal calprotectin	58 UC patients	MUC > 6.2 predicted 1 year relapse (HR: 3.22)
Goodsall *et al*[4]	Prospective cohort	8 wk	Milan criteria, BWT	NHI, colonoscopy (UCEIS score)	29 UC patients	IUS + FC accurately predicted histological activity in 88% of cases (sensitivity 88%, specificity 80%, positive predictive valve 95%, and negative predictive valve 57%)
Piazza *et al*[21]	Prospective, multi centre	11.5-31.9 mo	MUC, BWT	MES, FCP, CRP	141 UC patients	MUC > 7.7 was better in predicting colectomy (AUC: 0.83) risk than MES
Rispo *et al*[22]	Prospective	Cross-sectional	MUC	Colonoscopy (MES)	86 UC patients	Conventional and hand-held ultrasound had excellent agreement for MUC (kappa = 0.86). No difference in diagnostic accuracy (0.87 IUS *vs* 0.84 hand-held IUS)
Bots *et al*[23]	Prospective	3 wk	BWT, vascularity, haustrations, fat wrapping	Colonoscopy	60 UCpatients	UC-IUS score was developed which has strong correlation with endoscopic disease activity (ρ = 0.83 for Mayo score, ρ = 0.76 for UCEIS score)
Komatsu *et al*[24]	Retrospective validation	-	BWT, submucosal index	Colonoscopy	44 UC patients	High PPV (95%) and NPV (80%) to predict endoscopic improvement

CD: Crohn's disease; IUS: Intestinal ultrasound; FC: Faecal calprotectin; UC: Ulcerative colitis; MUC: Milan ultrasound criteria; CI: Confidence interval; HUS: Humanitas ultrasound criteria; CWF: Colon wall flow; CWT: Colon wall thickness; SUS-CD: Simple ultrasound score-Crohn's disease; IBUS-SAS: International bowel ultrasound-segmental activity score; BWT: Bowel wall thickness; CDAI: Crohn's disease activity index; DBE: Double balloon enteroscopy; US-CD: US scoring system for Crohn's disease; UC-IUS: Ulcerative colitis intestinal ultrasound; ρ: Spearman's rho; UCEIS: Ulcerative colitis endoscopic index of severity; PPV: Positive predictive value; NPV: Negative predictive value.

Table 3 Role of intestinal ultrasound in predicting response to therapy in ulcerative colitis

Ref.	Study type	Number of patients	Treatment agent(s)	IUS predictor(s)	Follow-up duration	Time points of IUS	Therapeutic outcomes
Dubbins [25]	Retrospective	9 UC (19 CD)	Steroid ± immunosuppressive therapy	BWT	2-4 mo	Baseline, 2-4 mo	No significant change in BWT in UC but there was significant response in CD
Maconi *et al*[38]	Prospective	30 active UC	Steroids	BWT	2 mo	Baseline and 2 mo	Significant reduction in BWT in clinical responders; IUS response significantly correlated with clinical biochemical and endoscopic activity
Yoshida *et al*[26]	Prospective	26 UC	Cytaphresis + conventional therapy	BWT	1 year	Baseline and 2-3 wk	Early IUS response (decrease in BWT by 2.5 mm at 2-3 wk) predicted 1 year response (91% *vs* 40%) lower relapse (9% *vs* 47%)
Goertz *et al*[27]	Prospective	7 UC	Vedolizumab	BWT, CDS, CEUS-amplitude and time derived parameters	14 wk	Baseline, 14 wk	Decrease in CDS intensity. Decrease in amplitude dependent CEUS parameters (peak enhancement and wash in rates)
Maaser *et al*[28]	Prospective, multi centre	224 UC	Steroid, anti-TNF, anti-integrin, AZA/6-MP	BWT, BWS, CDS, haustration, lymph nodes, inflammatory fat, ascites	16 wk	Baseline, 2, 6, and 12 wk	Significant improvement in IUS parameters was seen as early as 2 wk. Significant correlation of normalisation of BWT at 12 wk with clinical improvement and biomarkers
Les *et al* [29]	Prospective	28 UC (89 CD)	5-ASA, budesonide, AZA, anti-TNF	BWT, BWS, CDS, i-fat, lymph nodes	6 mo	Baseline	Predictors (overall IBD); immediate treatment escalation (31.7%) Score = 1/[1 + Exp (-XB)] where XB = 0.75 × [BWT (mm)] + 3.5 × (CDS = 1) – 7.31; AUC: 0.94, score > 0.5 100% sensitivity, 83% specificity; subsequent treatment escalation (17.9%), AUC: 0.92; Score = 1/[1 + Exp (-XB)] where XB = 0.8X [bowel wall thickness (mm)] - 1.3X (Presence of wall stratification =1) – 3.82 Score > 0.6 has 90% sensitivity, 86.4% specificity
Smith *et al* [30]	Retrospective	23 CD, 8 UC (22 CD and 7 UC on biologics)	Anti-TNF, ustekinumab, vedolizumab	BWT, CDS	46 wk	2, 6, and 14 wk	16% improvement in BWT at 6 wk and 10% improvement at wk 14 predicted treatment persistence/response at 46 wk
Vaughan *et al*[31]	Prospective	79 UC and 24 CD	Maintenance infliximab	BWT, CDS	Cross-sectional (median disease duration 8 years)	Cross-sectional data	Lower infliximab trough level was associated with higher CDS in both UC and CD
Helwig *et al*[32]	*Post-hoc* analysis of prospective, multi centre studies	131 UC (118 CD)	Standard of care	BWT, CDS, BWS, i-fat, transmural healing, transmural response	52 wk	0, 12, 52 wk	76.6% TR and 45%-61.4% TH at 12 wk after treatment intensification
de Voogd *et al*[33]	Longitudinal, prospective	30 UC on tofacinib	Tofacitinib	BWT	8 wk	Baseline and 8 wk	Most accurate BWT cut-off for endoscopic remission was 2.8 mm; for endoscopic response: 3.9 mm and > 32% decrease in BWT

Ilvemark *et al*[34]	Blinded, prospective multi centre, observational	56 acute severe UC	IV steroid	BWT	48 h and 6 d	Baseline, 48 ± 24 h and 6 ± 1 d	≤ 20% reduction in BWT has 84.2% sensitivity and 78.4% specificity for determining non-response (AUC: 0.85)
Allocca *et al*[19]	Prospective	49 UC	Infliximab, adalimumab, vedolizumab, ustekinumab	Milan ultrasound criteria based on BWT and CDS intensity	1 year	Baseline, week 12, and 1 year	MUC ≤ 6.2 at week 12 independent predictor of MES ≤ 1; A ≥ 2 reduction in MUC predicted MES = 0
de Voogd *et al*[33]	Prospective, single center	51 UC patients	Steroids, 5-ASA, thiopurines, biologics, tofacitinib, cyclosporin	BWT, CDS, haustrations, BWS, fat wrapping, lymph nodes	26 wk	Baseline, week 2, week 6, weeks 8-26	BWT and CDS at weeks 2 and 6 predicted endoscopic remission and response at 8-26 wk

CD: Crohn's disease; TNF: Tumor necrosis factor; TH: Transmural healing; BWT: Bowel wall thickness; CDS: Color doppler signal; IUS: Intestinal ultrasound; CEUS: Contrast enhanced ultrasound; TI: Terminal ileum; RCT: Randomized controlled trial; IFX: Infliximab; SWE: Shear wave elastography; SUS-CD: Simple Ultrasound Activity Score for CD; IBUS-SAS: International Bowel Ultrasound Segmental Activity Score; BUSS: Bowel Ultra-Sound Score; SICUS: Sall Intestine Contrast Ultrasonography.

More recently, IUS was shown to be a good surrogate marker for endoscopic response and remission in moderate to severe UC. In a study, 30 patients started on tofacitinib induction therapy were monitored using IUS, colonoscopy, and Robert's histological index (RHI) at baseline and after 8 wk. BWT cutoffs of 2.8 mm and 3.9 mm had excellent accuracy (AUC > 0.85) for endoscopic remission (MES 0) and improvement (MES ≤ 1), respectively. A decrease in BWT by 32% correlated with the endoscopic response (decrease in MES ≥ 1). Among the wall layers, the submucosa was most responsive to change. BWT correlated with both MES and RHI[2]. Another recent, single-center, prospective observational study showed that MUC < 6.2 at 12 wk can effectively rule out endoscopic activity at 1 year (NPV 96%) in UC on biologic therapy. A 2-point decrease in MUC predicted eMS ≤ 1 with an 89% sensitivity and 71% specificity[19]. A prospective study demonstrated that BWT, CDS, and submucosal thickness (SMT) predicted endoscopic parameters (improvement and remission) by 6 wk. Hence, IUS can be used as a surrogate marker for endoscopy. BWT was reduced significantly at 2 wk in patients on infliximab and tofacitinib whereas it took longer time (6 wk) for vedolizumab. After 8 wk, there was no difference between the different agents regarding changes in BWT[33].

IUS in acute severe UC: Two studies have addressed the role of IUS in hospitalized patients with severe UC requiring intravenous steroids. A prospective, blinded, Danish, multi-center study (n = 56) showed that a > 20% reduction in BWT (mostly in sigmoid) at 48 ± 24 h after IV steroid predicted clinical response (partial Mayo score decrease > 30%) and need for rescue therapy at day 7[34]. Similarly, a single-center, retrospective study in pediatric severe UC (n = 52) showed that colonic BWT > 3.4 mm and loss of colonic wall stratification independently predicted steroid resistance when assessed within day 3 of hospitalization[35]. A recent study has shown that MUC can predict severity (cut-off > 8.54 for severe UC, sensitivity: 64.3%, specificity: 93.3%), corticosteroid failure (MUC > 10.54, sensitivity: 50%, specificity: 90.9%), and colectomy (MUC > 12.5, sensitivity: 55.6%, specificity: 97%) in UC[36].

IUS to detect appendiceal inflammation in UC: Regardless of the extent of UC, IUS findings of transverse appendicular diameter ≥ 6 mm are seen in 43% of patients with active UC (in the absence of clinical appendicitis) (n = 35) compared to 6% and 0% with quiescent (n = 30) and inactive disease (n = 30) as shown in a prospective study. The submucosal wall thickness is also increased in UC (1 mm in active and quiescent disease) compared to 0.7 mm in healthy controls[37]. The finding implies that IUS might help to select patients who would benefit from an appendectomy. However, future

validation is warranted by incorporating histologic findings in appendectomy specimens.

Mesenteric blood flow and UC activity: Earlier studies (4 prospective studies) recognized changes in mesenteric blood flow patterns in active UC[38-41]. The common theme in these studies was an increase in blood flow (both volume and velocity) and low pulsatility/resistance index in the mesenteric vessels, a differential increase in blood flow based on the location of colonic active disease (superior mesenteric artery for right colon and inferior mesenteric artery for left colon) (Table 4)[38-41]. However, the clinical usefulness of such findings is currently questionable.

CEUS: Three studies (2 prospective and 1 retrospective) evaluated CEUS in UC/IBD. The retrospective study was discussed earlier by Zhang *et al*[11] for differentiation of colonic cancer and IBD. CEUS can predict treatment response as discussed earlier for vedolizumab with a significant decrease in amplitude-dependent parameters in responders (Table 5)[27]. Increased vascularity in CEUS correlated histologically with increased vascular density (CD34+)[42].

Correlation of IUS with other modalities

Several clinical indices in UC correlate with IUS. Apart from clinical indices, IUS correlated with biomarkers and even histological activity (Table 6).

Correlation with biomarkers (*e.g.*, FCP/C-reactive protein): A recent retrospective study has shown that FCP and C-reactive protein (CRP) levels significantly correlated with the number of segments with active inflammation/complications and IUS scores (Table 7). The highest accuracy was seen for FCP cut-off 150 μg/g (AUC: 0.756) [concordance with active small bowel (n = 33), large bowel (n = 3), and combined disease (n = 24) were 72.7%, 66.7%, and 70.8%, respectively][43]. FCP also correlated with vascularity on color Doppler[44]. Another retrospective study (n = 213) showed that leucine-rich glycoprotein (> 14.6 μg/mL) was a better marker than CRP to predict active IUS findings for CD in clinical remission[45]. Another recent study showed that a combination of fecal immunochemical testing (FIT) > 100 ng/mL and BWT > 2 mm predicted mucosal inflammation (MES > 0) with good accuracy (AUC: FIT: 0.93, BWT: 0.84-0.97)[46].

Correlation with colonoscopy: The correlation between colonoscopy and IUS has been evaluated in 26 studies (7 retrospective, 19 prospective) in UC (Table 8)[14,20,47-64]. The sensitivity, specificity, accuracy, PPV, and NPV of IUS as compared to colonoscopy as gold standard varied from 50%-100%, 23%-100%, 83%-93.3%, 92%-100%, and 73%-100%, respectively (Table 8)[47,48,53,58,61,63]. Different time intervals between IUS and colonoscopy, study design (retrospective/prospective, including CD), and variable sample size may account for the widespread variation. The sensitivity, specificity, PPV, and NPV decreased from 100% (all with same-day colonoscopy) to 92%, 86%, 92%, and 86% when colonoscopy was done within 30 d[58]. The sensitivity, specificity, PPV, NPV, and agreement with colonoscopy for disease extent in UC were 92%, 80%, 88%, 86%, and 0.7, respectively[58]. There was a significant correlation between IUS (MUC, UC-IUS) and colonoscopic scores (MES, UCEIS)[20,23,51,54,60,62-64]. The correlation between MUC and MES varied between 0.61-0.653 (highest in severely affected areas: 0.88)[20]. The specificity of MUC to predict endoscopic activity increased from 94% (> 6.2) to 100% (> 8.2) with no incremental benefit of FCP[17]. Similarly, the correlation between MUC and UCEIS varied between 0.32-0.648[63]. UC-IUS had a higher correlation with endoscopic scores than MUC (MES: 0.83, UCEIS: 0.76)[23]. In pediatric UC, UC-IUS (sensitivity: 88%-100%, specificity: 84%-87%) was better than Civitelli index (sensitivity: 65%-80%, specificity: 89%-93%) [significantly better in ascending colon (AUC 0.82 *vs* 0.76) and transverse colon (AUC 0.88 and 0.77) but not in sigmoid (AUC both 0.84)][64]. MUC > 6.2 calculated by hand-held IUS (dual probe 5-7.5 MHz) (V san, General Electric Co.) had an 84% accuracy (highest in sigmoid colon and lowest in rectum)[22]. SWE showed a significant negative correlation (-0.404) with UCEIS[62]. IUS scores after 3 mo of high-dose steroids in severe UC also correlated with future risk of endoscopic activity at 15 mo[50,51]. In a recent study, the median FCP was lower in those with inactive IUS (median 50 μg/g) as compared to active IUS (270 μg/g).

Among the IUS parameters, BWT had the most consistent correlation with colonoscopic findings in the majority of studies[20,49,52,55,57,60,61]. BWT cut-offs of 2.1 mm, 3.2 mm, and 3.9 mm could differentiate Mayo 0 *vs* Mayo 1-3 (sensitivity: 82.6%, specificity: 93%, AUC: 0.91), Mayo 0-1 *vs* Mayo 2-3 (sensitivity: 89.1%, specificity: 92.3%, AUC: 0.946), and Mayo 3 *vs* others (sensitivity: 80.6%, specificity: 84.1, AUC: 0.909)[23]. In response to tofacitinib therapy, cut-off values of BWT for endoscopic remission (MES = 0), improvement (MES ≤ 1), and response (MES ≥ 1 decrease) were 2.8 mm (AUC 0.87, sensitivity 73%, specificity 100%), 3.9 mm (AUC 0.92, sensitivity 81%, specificity 100%), and 32% decrease (AUC 0.87, sensitivity 71%, specificity 90%), respectively[2]. In pediatric UC, BWT cut-offs of 2.9 mm in the colon and 2.5 mm in the ileum had excellent accuracy[49]. Change in BWT correlated well with change in endoscopic scores in the sigmoid (MES: 0.50, UCEIS: 0.68) and descending colon (MES: 0.67, UCEIS: 0.50)[2]. Combination of BWT < 3.75 mm and SMI (SMT divided by BWT%) < 49.7 has a sensitivity, specificity, PPV, NPV, and accuracy of 70%, 97.7%, 95.5%, 82.7%, and 86.5%, respectively[61]. Additionally, two studies showed a significant correlation between CDS and IUS activity (OR: 2.49-26.23)[14,59]. The correlation of CDS with MES was 0.98 (*c.f.*, BWT: 0.88, MUC: 0.88) in the worst affected segment[20].

Anteroposterior diameter of ≥ 12 mm and the presence of intra-luminal vascular signals correlated with pseudopolyposis in a small series (n = 12, both UC and CD) with a high sensitivity (75%) and specificity (100%)[65].

Correlation with cross-sectional imaging: The correlation between IUS and MRE findings has been studied mainly in CD. However, two prospective studies (one in IBD and another in suspected pediatric IBD) compared IUS and MRI (Table 9). The accuracy of IUS in the large bowel was 70% with MRI as the gold standard with a 100% correlation for active disease[56]. In suspected pediatric IBD, the sensitivity of IUS and magnetic resonance (MR) colonography was

Table 4 Summary of studies on superior mesenteric artery/inferior mesenteric artery artery flow in evaluating inflammatory bowel disease activity

Ref.	Study type	Number of patients	Parameters studied
Ahmed *et al*[41]	Prospective	84 UC (16 CD, 50 normal)	SMA and IMA PSV and EDV significantly higher in UC compared to controls; pulsatility index significantly higher in control group than UC
Maconi *et al*[38]	Prospective	24 UC (31 CD, 10 IBS)	Higher portal and mesenteric blood flow with lower RI of SMA was noted in active UC as compared to quiescent UC
Mirk *et al* [39]	Prospective	22 UC, 24 CD	IBD with active disease in left colon presented increases in flow velocity and flow volume with decrease in pulsatility index
Sığirci *et al*[40]	Prospective	44 (25 active, 19 inactive, 22 healthy)	IMA blood flow volume, mean PSV, ESV, mean velocity, and vessel diameter were higher and pulsatility index lower in active disease compared to quiescent disease; active disease in left colon had high higher mean PSV and velocity in IMA; mean EDV higher with lower mean PI and RI in SMA for those with pancolonic involvement

SMA: Superior mesenteric artery; CD: Crohn's disease; IMA: Inferior mesenteric artery; PSV: Peak systolic velocity; EDV: End diastolic velocity; UC: Ulcerative colitis; ESV: End systolic velocity; RI: Resistive index; PI: Pulsatility index; IBS: Irritable bowel syndrome; IBD: Inflammatory bowel disease.

Table 5 Summary of studies on contrast enhanced ultrasound in ulcerative colitis

Ref.	Study type	Number of patients	Parameters studied
Romanini *et al*[42]	Prospective	18 UC, 15 CD	High vascular density (CD34+; > 265 vessels per high power field, 40 ×) correlated with CEUS (higher and early peak, higher blood flow and volume)
Goertz *et al* [27]	Prospective	7 UC, 11 CD	Decrease in amplitude dependent CEUS parameters (peak enhancement and wash in rates). Time dependent parameters (*e.g.*, time to peak) remained stable
Zhang *et al* [11]	Retrospective	13 IBD, 38 colon cancer	Disordered and heterogeneous enhancement in colon cancer (95% and 79%) compared to IBD (9% and 0%). Colon cancer: Later enhancement, slower washout with lower speed to peak intensity

CD: Crohn's disease; IBD: Inflammatory bowel disease.

similar (55% IUS, 57% MR) whereas IUS was more specific (100% IUS *vs* 75% MR). Differentiation between UC and CD was not possible with either method except in cases where the terminal ileum was involved[8].

Correlation with histology: An earlier single-center, cross-sectional study showed that dynamic tissue perfusion in the inflamed intestine positively correlated with crypt abscess, neutrophils, and lymphocytic invasion, whereas it negatively correlated with wall edema[66]. Similarly, another prospective study showed that vascular density on histology was associated with CEUS parameters (higher and earlier peak, higher blood flow and volume)[42]. More recently, IUS grade based on BWT, CDS, BWS, and wall echogenicity correlated with Matt's histological grade (r = 0.35)[54]. MUC positively correlated with Nancy histological index (NHI) (r = 0.11). MUC > 6.3 and/or FCP ≥ 100 μg/g had a sensitivity of 88% and specificity of 90% for predicting NHI > 1 (Table 10)[4]. Rectal BWT > 4 mm on trans-perineal ultrasonography (USG) had a higher sensitivity (95.5% *vs* 59.1%) but lower specificity (41.6% *vs* 76.2%) than Limberg's score > 2 to predict NHI > 1 [57].

IUS and TH

TH is a therapeutic target in the "treat to target strategy" of CD; however, it can be evaluated in UC as well by IUS[32]. Sonographic assessment of TH has the potential to replace cross-sectional imaging for documentation of TH and make it part of routine practice. TH has been shown to predict relapse/steroid/treatment escalation-free survival[67]. A *post-hoc* analysis of prospective studies has used three definitions of TH and found that TR (≥ 25% reduction or normalization of BWT) was achieved in 76% of UC cases while TH was achieved in 45%-61%[32].

IUS in special populations

IUS in pediatric population: There is growing literature on the role of IUS in children (Table 11)[7,8,47-49,64,68,69]. IUS is preferable in pediatric IBD/UC over colonoscopy and MRI given high patient and caregiver satisfaction as shown in a recent study[69]. A noninvasive monitoring strategy using IUS, FCP, and colon capsule endoscopy has good tolerability with high accuracy as compared to colonoscopic monitoring[70]. We have found 12 studies evaluating the role of IUS in pediatric UC/IBD. Among them, seven evaluated the accuracy of IUS in comparison to ileo-colonoscopy with or without MR colonography (Table 11)[8,47-49,71]. IUS was highly accurate in assessing the location and endoscopic (77% sensitivity, 83% specificity) and histologic severity (75% sensitivity and 82% specificity) of the disease[47]. The cut-off for

Table 6 Summary of studies correlating clinical activity with intestinal ultrasound

Ref.	Study type	Number of patients	IUS predictors	Clinical score	Parameters studied
Goodsall *et al*[4]	Prospective	19 UC (29 paired data)	MUC	SCCAI, Mayo score	Mayo score: $r = 0.307$; 95%CI, 0.020-0.595; $P = 0.036$; SCCAI score: $r = 0.04$; 95%CI, −0.21 to 0.28; $P = 0.768$
Kinoshita *et al*[54]	Prospective, multi-centre	156 UC	Ultrasound severity score based on BWT, BWS, hypoechoic/hyperechoic changes in submucosa/mucosa	Rachmilewitz clinical activity index	$r = 0.40$, $P < 0.001$
Lim *et al* [63]	Prospective cross-sectional	29 UC, 22 CD	BWT, CDS, BWS, i-fat	Partial Mayo score	$r = 0.192$, $P = 0.317$
Maaser *et al*[28]	Prospective, multi-center	224 UC	BWT	SCCAI	Sigmoid colon: Baseline: $r = 0.187$; 12 wk: $r = 0.547$; descending colon: Baseline: $r = 0.262$; 12 wk: $r = 0.5$
Saleh *et al* [89]	Retrospective	39 UC, 108 DC	BWT, CDS, i-fat, BWS, lymph node, free fluid, haustartion, motility	Mayo score, UCAI	$r = 0.016$ Mayo score ($P = 0.002$); UCAI ($P = 0.014$)
de Voogd *et al*[2]	Prospective, single centre	16 UC, 22 CD	BWT, CDS, haustrations, BWS, fatty wrapping	SCCAI, Lichtiger index	SCCAI and BWT in the SC ($r = 0.65$, $P < 0.0001$) and DC ($r = 0.59$, $P < 0.002$). Lichtiger score and BWT SC ($r = 0.65$, $P = 0.001$) and DC ($r = 0.63$, $P = 0.001$)
Yamada *et al*[62]	Prospective	26	SWE, SWD	UCEIS	Negative correlation with SWE ($r = -0.505$, $P = 0.008$); no correlation with ($r = 0.001$, $P = 0.998$)

CD: Crohn's disease; UC: Ulcerative Colitis; SWE: Shear wave elastography; UCEIS: Ulcerative colitis endoscopic activity index; CDAI: Crohn's disease activity index; BWT: Bowel wall thickness; UCAI: Ulcerative colitis activity index; MUC: Mayo ultrasound score.

BWT was lower than for adults. The accuracy of the 1.9 mm cut-off was 0.743 (AUC) (sensitivity: 64%, specificity: 76%) which needs further validation[72]. IUS has a good correlation with MRE and colonoscopy on the location and severity of disease[8,72]. Various IUS scores for pediatric UC and CD have been described which need external validation. For UC, The UC-IUS score was better than the Civitelli index[64]. The sum of adjusted BWT was shown to be better than FCP in predicting moderate colonic inflammation (Mayo 2) in children with UC[73]. A study evaluated the role of IUS in predicting steroid responsiveness in pediatric acute severe UC as discussed earlier[35]. A combination of grayscale, color Doppler, and shear wave ultrasound was shown to increase diagnostic accuracy (92%) with a 100% sensitivity in an observational study[74]. In a study in pediatric UC ($n = 12$), dynamic tissue perfusion measurement (calculated from color Doppler videos using software to calculate perfusion velocity and perfused area) positively correlated with histologic findings of inflammatory cell infiltration and inversely correlated with wall edema (Table 11)[66].

IUS in pregnancy: IUS can be valuable in IBD disease monitoring for pregnant women, being non-invasive and radiation-free. In a prospective cohort study (16 UC, 22 CD), it was shown that the feasibility of IUS decreases significantly in the third trimester due to the gravid uterus especially in the sigmoid colon (96% to 69%) and terminal ileum (91% to 22%). IUS had a good correlation with clinical activity ($r = 0.60$) and FCP ($r = 0.73$). IUS identified active disease with an 84% sensitivity and 98% specificity. Treatment response was detected with an 80% sensitivity and 92% specificity[75]. A case series ($n = 5$, UC post-ileal-pouch anal anastomosis [IPAA]) has shown that FCP and IUS can help detect inflammatory pouch complications in pregnancy after ileal-pouch anal anastomosis, avoiding pouchoscopy[76].

IUS in IBD management during coronavirus disease 2019 pandemic: Bedside, IUS could lead to a change in clinical management in up to 80% of IBD patients with acute symptoms or suspected IBD as shown in a prospective, observational study during the coronavirus disease 2019 (COVID-19) pandemic when access to endoscopic services was limited [77]. Another prospective, multi-center study showed that point-of-care IUS in urgent care pathway showed active disease in 65% of cases, resulting in acute change in management in 57% and avoiding/delaying colonoscopy in 85%[72]. This highlighted the potential of IUS to improve care delivery without exhausting acute care services.

Trans-perineal and transvaginal USG: Trans-perineal ultrasound (TPUS) with microconvex or linear probes has shown that rectal wall thickness ≤ 4 mm predicted endoscopic (AUC = 0.90) and histological (AUC = 0.87-0.89) healing with high accuracy and was better than FCP[57]. Moreover, a decrease in rectal wall thickness within 1 wk assessed by TPUS predicted clinical remission at 8 wk (Table 12)[78].

The usefulness of transvaginal sonography (TVS) has been described for evaluating rectal involvement in UC and evaluation of rectal/perianal CD in select parous females in a small series ($n = 20$, UC-8) with matched controls (TVS done for gynecological indications). Rectal wall thickness (> 5 mm) and modified Limberg score ≥ 1 predicted endoscopic activity with high accuracy (AUC: 0.968 and 1, respectively)[79].

Table 7 Summary of studies correlating blood (C-reactive protein/erythrocyte sedimentation rate) or fecal biomarkers (fecal calprotectin) with intestinal ultrasound in ulcerative colitis

Ref.	Study type	Number of patients	IUS comparator	Biomarker(s)	Time between IUS and biomarker testing	Conclusion
Bots *et al*[23]	Retrospective, single centre	65 UC (280 CD)	BWT, CDS, BWS, i-fat, haustrations, lymph nodes, motility	FCP, CRP	Within 1 wk	Higher FCP and CRP in IUS active disease Median FCP Active disease: 1720 μg/g; Inactive disease: 75 μg/g ($P < 0.001$); Median CRP Active disease: 3.6 mg/L; Inactive disease: 1.8 mg/L ($P < 0.076$)
Goodsall *et al*[4]	Prospective	19 severe UC (29 paired data)	BWT, CDI, BWS	FCP	Baseline	Log converted FCP had significant correlation with NHI ($r = 0.027$, 0 = 0.044), but not with MUC ($r = 0.01$, $P = 0.064$); Composite of MUC and FCP has 88% sensitivity, 80% specificity, 95% PPV, and 57% NPV ($P = 0.007$)
Ilvemark *et al*[34]	Blinded, prospective multi centre, observational	56 acute severe UC	BWT	CRP	Baseline	FCP is not a predictor of IV steroid response; BWT has significant association with CRP at 48 ± 24 h, $r = 0.47$, $P < 0.005$
Les *et al*[29]	Prospective	28 UC, 89 CD	BWT, loss of stratification, CD, mesenteric hypertrophy, lymph nodes	CRP, FCP	Baseline	FCP predicted immediate (AUC 0.86) and subsequent treatment intensification (AUC 0.81); CRP predicted immediate (AUC 0.81) and subsequent treatment intensification (AUC 0.55)
Lim *et al*[63]	Prospective cross-sectional	29 UC, 22 CD	BWT, BWS, vascularity, mesenteric fat, complications	FCP, CRP	Baseline	IUS parameters have good correlation with FCP ($r = 0.489$, $P < 0.01$) and CRP ($r = 0.604$, $P < 0.01$) significant
Maaser *et al*[28]	Prospective, multicentre	224 UC	BWT	FCP	Baseline, 2, 6, 12 wk	At 12 wk, 16% with increased BWT had FCP < 250 μg/g and 44.4% with normal BWT had FCP ≥ 250 μg/g
Sagami *et al*[57]	Single centre, prospective, cross-sectional	53 UC	BWT, CDS (rectum)	FCP	Baseline	BWT better than FCP (> 50 μg/g) for predicting histologic and endoscopic activity (MES > 1) in rectum by trans-perineal ultrasound; CDS not better than FCP
Sagami *et al*[78]	Prospective, single centre	100 UC	BWT, CDS (rectum)	FCP, CRP	Baseline 1, 8 wk	FCP and CRP were not independent predictors of remission at 8 wk; BWT and CDS were independent predictors of remission at 8 wk
Saleh *et al*[89]	Retrospective	39UC, 108 CD	BWT, BWS, CDS, mesenteric fat, complications	FCP, CRP	Baseline	54% of those with combined clinical and biochemical remission (ESR ≤ 40 mm/h and CRP ≤ 10 mg/L and FCP ≤ 50 μg/mg and fecal lactoferrin ≤ 30 μg/mL) had active IUS findings; 67% without combined remission had active IUS findings
de Voogd *et al*[2]	Prospective, single centre	16 UC, 22 CD	BWT, CDS, loss of haustration, bowel wall stratification, fatty wrapping	FCP	Baseline	Addition of FCP, decrease of FCP, or cutoff values for FCP did not improve the multivariate model (BWT, haustrations) to detect endoscopic remission, improvement, or response
St-Pierre *et al*[90]	Prospective, multicenter, observational cohort	18 UC, 123 CD	BWT, CDS	FCP	Baseline	Median FCP: IUS inactive inflammation: 50 μg/g, active inflammation 270 μg/g
Castellano *et al*[44]	Retrospective	44 pediatric IBD	CDS	FCP	Baseline	Median FCP low (median 92 μg/g) for low Doppler flow (≤ 2 /cm^2) and high (median 2286 μg/g) for high Doppler flow (≥ 3 /cm^2)

FCP: Fecal calprotectin; CDS: Color Doppler Signal; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn' disease; IUS: Intestinal ultrasound; BWT: Bowel wall thickness; NPV: Negative predictive value; CRP: C-reactive protein.

Table 8 Summary of studies evaluating correlation of colonoscopy and intestinal ultrasound in ulcerative colitis

Ref.	Study type	Number of patients	Treatment	IUS predictors	Colonoscopy score	Follow-up duration	Time points of IUS	Correlation with colonoscopy
Borthne *et al* [48]	Prospective	UC 4, CD 17 (pediatric)	NA	BWT, length, CDS, lymph nodes	-	Cross-sectional	Baseline	Sensitivity and diagnostic accuracy of IUS as compared to endoscopy: 93.3%
Bremner *et al* [49]	Prospective	12 UC (25 CD, 1 in determinate colitis, 6 normal	NA	BWT	Subjective assessment	Cross-sectional	Baseline	Colonic BWT > 2.9: Sensitivity for moderate/severe disease: 48%, specificity: 93%, PPV: 83%; ileal BWT > 2.5 mm: Sensitivity for moderate/severe disease: 75%, specificity: 92%, PPV: 88%
Chavannes *et al*[72]	Cross-sectional, single centre	33 children with suspected IBD (11 UC)	NA	Ileo-colonoscopy	UCEIS	Cross-sectional	Baseline	Colonic BWT > 1.9 mm: AUC: 0.743, sensitivity: 64%, specificity: 76% to detect inflamed bowel; agreement with colonoscopy: Prediction of IBD: 69.7%, kappa = 0.52; distribution of disease: 45.5%, kappa = 0.48
Haber *et al*[47]	Prospective	21 UC pediatrics (26 CD, controls)	NA	BWT, BWS, wall echo pattern	No, mild, severe	Cross-sectional	Baseline	AUC: 0.743, sensitivity: 64%, specificity: 76% to detect inflamed bowel
Parente *et al* [50]	Prospective	83 moderate to severe UC	High dose systemic steroids	BWT, CDS	Baron score	15 mo	Baseline, 3, 9, and 15 mo	Agreement with colonoscopy: Prediction of IBD: 69.7%, kappa = 0.52; distribution of disease: 45.5%, kappa = 0.48
Parente *et al* [51]	Prospective	83 moderate to severe UC	Same as above	BWT, CDS	Baron score	15 mo	Baseline, 3, 9, and 15 mo	Similar result as the study above
Yamada *et al* [62]	Prospective	26 UC	NA	SWE, SWD	UCEIS	Cross-sectional	-	SWE and UCEIS correlation: r = -0.404, P = 0.041. No significant correlation between SWD & UCEIS
Carter *et al*[53]	Retrospective	11 UC (167 CD)	NA	BWT, BWS, CDS, wall echogenicity, i-fat	NA	Cross-sectional	Baseline	Sensitivity 90%, specificity: 23% as compared to colonoscopy/MRE (combined CD and UC)
Antonelli *et al* [52]	Retrospective	51 moderate to severe UC	NA	BWT > 4 mm	Mayo score	Cross-sectional	-	BWT strongly correlated with CRP and endoscopic score
Allocca *et al* [16]	Prospective	53 UC	NA	BWT > 3 + CDS; BWT > 4.43 + no CDS	Mayo endoscopic score	Cross-sectional	Baseline	Sensitivity: 68%, specificity: 100%, accuracy: 83%, PPV: 100%, NPV: 73%
Kinoshita *et al* [54]	Prospective, multi centre (n = 5)	156 UC	NA	BWT, BWS, wall echogenicity	Matt's endoscopic classification	Cross-sectional	Baseline	Significant concordance between maximum grades (kappa = 0.47) and grades among all colonic segments (kappa = 0.55)
Luo *et al*[14]	Retrospective	50 UC, 50 CD, and 50 controls	NA	CDS	Active *vs* remission	Cross-sectional	Baseline	Higher Limberg's score in active disease (odds ratio: 26.325, P < 0.05)
Sathananthan	Prospective,	39 UC (35 CD)	5-ASA, immunomod-	BWT, CDS	MES	Cross-	Same day or	Same day colonoscopy (sensitivity 100%, specificity 100%, PPV 100%, NPV 100%,

et al[58]	single centre		ulator, biologics, steriods			sectional	within 30 d	kappa = 1); colonoscopy within 30 d (sensitivity 92%, specificity 86%, PPV 92%, NPV 86%, kappa = 0.77 (MES ≥ 1). Extent: Sensitivity 92%, specificity 80%, PPV 88%, NPV 86%, kappa = 0.7
Sagami *et al* [57]	Single centre, prospective, cross-sectional	53 UC	5-ASA, immunomodulators, budesonide, anti-TNF	BWT, BWS, CDS	MES	Cross-sectional	Baseline	BWT > 4 mm trans-perineal USG (sensitivity: 100%, specificity: 45.8%, AUC: 0.904) to predict MES, better than trans-abdominal ultrasound (sensitivity: 96.3%, specificity: 12.5%, AUC: 0.667). Correlation of MES with rectal BWT (trans-perineal US): BWT and MES: $r = 0.7204$, $P < 0.0001$; CDS and MES: $r = 0.6619$, $P < 0.0001$
Kamel *et al*[56]	Prospective	14 UC (26 CD)	NA	BWT, CDS, BWS, i-fat, lymph nodes, stricture, abscess	NA	Cross-sectional	Baseline	100% agreement between colonoscopy and IUS
Allocca *et al* [17]	Prospective	43 UC	Details not available	BWT, CDS	Mayo endoscopic score	Cross-sectional	Baseline	MUC > 6.2 discriminated active UC (sensitivity 85%, specificity 94%, AUC 0.902); MUC > 8.2 100% specific; FCP no incremental value
Zhang *et al*[59]	Retrospective	103 UC	NA	BWT, CDS	Mayo endoscopic score	Cross-sectional	Baseline	Prediction of endoscopic activity: BWT: Not significant; CDS: OR = 2.492, $P < 0.001$
Bots *et al*[23]	Prospective	60 UC	Conventional therapy, biologic, tofacitinib, topical tacrolimus	BWT, vascularity, haustrations, fat wrapping	Mayo endoscopic score, UCEIS	Cross-sectional	Baseline	UC-IUS score has strong correlation with endoscopic disease activity (ρ = 0.83 for Mayo score, ρ = 0.76 for UCEIS score); BWT > 2.1 for Mayo 0 *vs* Mayo 1-3: Sensitivity: 82.6%, specificity: 93%, AUC: 0.91. BWT > 3.2 for Mayo 0-1 *vs* Mayo 2-3: Sensitivity: 89.1%, specificity: 92.3%, AUC: 0.946. BWT > 3.9 mm for Mayo 3 *vs* others: Sensitivity: 80.6%, specificity: 84.1, AUC: 0.909
Allocca *et al* [18]	Prospective	98 UC	NA	BWT, CDS	MES	Cross-sectional	Baseline	Significant correlation between MES and MUC ($r = 0.653$)
Bots *et al*[23]	Retrospective, single center	65 UC (280 CD)	Biologics, conventional therapy	BWT, CDS, BWS, i-fat, haustrations, lymph nodes, motility	MES	Cross-sectional	Baseline	Agreement with endoscopy: 86.3%. Correlation: 0.70. Kappa agreement: 0.61 (both UC and CD)
Miyoshi *et al* [61]	Retrospective	24 UC (31 CD, 10 IBS)	NA	BWT, BWS, CDS, modified Limberg's score, SMI	MES	Cross-sectional	≤ 15 d between IUS and colonoscopy	BWT < 3.75 mm and SMI < 49.7: Sensitivity: 70%, specificity: 97.7%, PPV: 95.5%, NPV: 82.7%, accuracy: 86.5%
de Voogd *et al* [2]	Prospective	30 UC	Tofacitinib	BWT	MES and UCEIS	8 wk	Baseline and 8 wk	BWT correlated with MES and UCEIS. Cutoff values for BWT: (1) 2.8 mm for endoscopic remission (AUC: 0.87, 95%CI: 0.74-1.00, $P = 0.006$) (sensitivity 73%, specificity 100%); (2) 3.9 mm for improvement (AUC: 0.92, 95%CI: 0.82-1.00, $P < 0.0001$) (sensitivity 81%, specificity 100%); and (3) Decrease of 32% for response (AUC: 0.87, 95%CI: 0.74-1.00, $P = 0.002$) (sensitivity 71%, specificity 90%). Correlation: ΔBWT and ΔMES: 0.50, $P = 0.009$; ΔBWT and ΔUCEIS: 0.68, $P < 0.0001$ (sigmoid); ΔBWT and ΔMES: 0.67, $P = 0.001$; ΔBWT and ΔUCEIS: 0.50, $P = 0.02$ (descending colon)
van Wassenaer *et al*[64]	Prospective cross-sectional	35 UC (pediatric)	NA	UC-IUS score, Civitelli index	Mayo endoscopic score	Cross-sectional	Baseline	UC-IUS score better than Civitelli index for both sensitivity (88%-100% *vs* 65-80%) and specificity (84%-87% *vs* 89-93%) (MES ≥ 2). Higher AUC in ascending colon (0.82 *vs* 0.76) and transverse colon (0.88 *vs* 0.77). No difference in descending colon (both 0.84)
Goodsall *et al*	Prospective	29 UC	NA	BWT, CDS, BWS,	UCEIS	Cross-	Baseline	MUC had significant correlation with UCEIS ($r = 0.32$; 95%CI: 0.14-0.49; $P < 0.001$)

[4]				MUC		sectional		
Lim *et al*[63]	Prospective cross-sectional	29 UC (22CD)	NA	BWT, BWS, i-fat, CDS	UCEIS	Cross-sectional	Baseline	Sensitivity: 50%, specificity: 100%, PPV: 100%, NPV: 84%; 100% sensitivity/specificity in transverse colon; correlation with endoscopic activity index: 0.648 ($P < 0.01$)
Maeda *et al* [20]	Retrospective	58 UC	5-ASA, topical therapy, anti-TNF, vedolizumab	BWT, CDS, BWS, enlarged lymph nodes, MUC	MES	3 mo	Baseline, 3, 6, 12 mo	MUC and MES: 0.61 (entire colon). Most severely affected segment: BWT and MES: 0.88; CDS and MES: 0.98; MUC and MES: 0.88. Accuracy of MUC > 6.2 to differentiate MES ≥ 1 and 0 (sensitivity: 24%, specificity: 100%, PPV: 100%, NPV: 0.47, AUC: 0.67)
Rispo *et al*[22]	Prospective	86 UC	5-ASA, steroids, IMS, biologics	Milan ultrasound criteria	Mayo endoscopic score	Cross-sectional	-	HHIUS MUC > 6.2: Sensitivity: 80%, specificity: 88%, PPV: 83%, NPV: 86%, accuracy: 84%; highest in sigmoid colon; lowest in rectum

TNF: Tumor necrosis factor; BWT: Bowel wall thickness; CDS: Color Doppler signal; IUS: Intestinal ultrasound; IUS: Intestinal ultrasound; SWE: Shear wave elastography; HHIUS: Hand-held intestinal ultrasound; 5-ASA: 5-amino salicylic acid; UC: Ulcerative colitis; PPV: Positive predictive value; NPV: Negative predictive value; IMS: Immunosuppressant; MUC: Milan ultrasound score; MES: Mayo endoscopic score; BWS: Bowel wall stratification; UCEIS: Ulcerative colitis endoscopic activity index; i-fat: Inflammatory fat; CD: Crohn's disease; CI: Confidence interval; AUC: Area under the curve; SMI: Submucosal index.

Gastroenterologist- or sonologist-led IUS

A pilot study showed that point-of-care IUS performed by gastroenterologists after limited training (200 supervised scans) can accurately identify disease activity and the extent, and presence of complications based on paired MRE ($n = 42$) and colonoscopy ($n = 38$)[80]. The cut-off for achieving competence to detect IBD complications (advanced competence) was shown to be even lower ($n = 97$) in a recent study (even lower in those with experience in gastrointestinal ultrasound, approximately 70)[81]. Similarly, after an existing IUS training curriculum, healthcare physicians could perform IUS with comparable diagnostic accuracy (AUC: 0.71-0.81) as radiologists (0.67-0.79)[68]. A feasibility study of 79 cases of suspected or established IBD showed that the sensitivity values of IUS to detect bowel wall thickening, stricture, and mass were 90%, 94%, and 75%, respectively, where cross-sectional imaging or endoscopic examination was done within 3 mo of IUS[53]. The sensitivity and specificity to detect active disease can be as high as 88% and 93%, respectively, even in a low-volume, non-expert center[82]. However, there are barriers to physician sonographers leading IUS service in IBD which include an unmet need for training opportunities, preference for alternate imaging modalities, lack of adequate support from management, increased workload, and protectionist behavior from radiologists. A United Kingdom survey showed that 70% of physician sonographers were not confident in doing IUS in IBD although there was high interest[83].

IOA with IUS: A study assessing IOA among six expert sonographers conducting IUS in 30 UC patients (25 active, 5 quiescent) showed perfect, substantial, moderate, and fair agreement for BWT (kappa = 0.96), CDS (kappa = 0.63), lymph nodes (kappa = 0.41), and inflammatory fat (kappa = 0.36)/bowel wall stratification (kappa = 0.24)/loss of haustrations (kappa = 0.26). The agreement for IUS disease severity and activity was perfect (kappa = 0.93) and substantial (kappa = 0.77), respectively[15]. In a study comparing the correlation of IUS with colonoscopy in UC ($n = 53$), the IOA between two expert operators was 0.83[84]. Another prospective study showed the highest IOA for terminal ileal wall thickness and the highest agreement for wall thickness (0.882) [> mesenteric hyperechogenicity (0.841) > wall stratification (0.685) > vascularity (0.681) > lymphadenopathy (0.633)][85]. The agreement (kappa) for the overall IUS score was 0.749 in another study with two experts blinded to clinical details[86]. In a study on IUS including children with suspected or established IBD in which physician gastroenterologists and radiologists performed IUS, the IOA (kappa) for disease activity in the terminal ileum, transverse colon, and descending colon was 0.58, 0.49, and 0.52, respectively[68]. An interesting prospective study evaluated IOA for new ($n = 11$) and relapsing CD ($n = 27$). The agreement for small bowel diseases was

Table 9 Summary of studies comparing intestinal ultrasound and magnetic resonance enterography

Ref.	Study type	Number of patients	Follow-up duration	Comparator	IUS parameters	Gold standard	Results
Kamel *et al*[56]	Prospective	40 (14 UC, 26 CD)	Cross-sectional	Bowel ultrasound and MRE	BWT, CDS, mesenteric fat and lymph nodes, complications	MRE and colonoscopy	Accuracy of IUS (in IBD): 85% ileum, 70% large bowel, 100% correlation with MRI/colonoscopy with respect to active disease (in IBD) (no separate analysis for UC)
Ziech *et al* [8]	Prospective	28 suspected IBD pediatric	Cross-sectional	MR colonography	BWT, CDS, BWS, i-fat, haustrations, lymph nodes, motility	MR colonography	Sensitivity IUS: 55%; MR colonography: 57%; Specificity IUS: 100%; MR colonography: 75%; cannot effectively differentiate UC and CD unless terminal ileum is involved
Barber *et al*[71]	Retrospective	53 children	Cross-sectional	MRE	Scoring based on METRIC trial	Combined consensus score based imaging and clinical scores	Clinical correlation of IUS score (0.657) > MRE score (0.598). Agreement for IUS scoring: Lin coefficient 0.95 > MRE 0.60

CD: Crohn's disease; UC: Ulcerative colitis; MRE: Magnetic resonance enterography; CTE: Computed tomography enterography; TI: Terminal ileum; BWT: Bowel wall thickness; BWS: Bowel wall stratification; AUC: Area under the curve; IBUS-SAS: International bowel ultrasound segmental activity score; HR-US: High resolution ultrasound.

Table 10 Summary of studies correlating histology with intestinal ultrasound

Ref.	Study type	Number of patients	Treatment	IUS predictors	Histologic score	Correlation
Scholbach *et al*[66]	Single center, cross-sectional	12 pediatric UC	NA	Dynamic tissue perfusion measurement (DTPM)	No score Parameters: crypt abscess, neutrophils and lymphocytic invasion, wall edema	Wall perfusion on DTPM positively correlated with crypt abscess, neutrophils, and lymphocytic invasion. Negative correlation with wall edema
Romanini *et al*[42]	Prospective	18 UC, 15 CD	NS	Peak intensity, time to peak, regional blood volume and flow	Vascular density	High vascular density (CD 34+; > 265 vessels per high power field, 40 ×) correlated with IUS and CEUS (higher and earlier peak, higher blood flow and volume)
Kinoshita *et al*[54]	Prospective	156 UC	NS	BWT, CDI, BWS, wall echogenicity	Matt's histological grade (1-5)	$r = 0.35$, $P < 0.001$
Sagami *et al* [57]	Single center, prospective, cross-sectional	53 UC	5-ASA, immunomodulators, budesonide, anti-TNF	BWT, BWS	Robarts histopathology index and Nancy histological index	Only BWT independently predicted histological activity in rectum; BWT > 4 highest sensitivity (95.5%), specificity 41.6%, and AUC 0.869 to predict NHI >1; specificity (76.2%) higher and sensitivity (59.1%) lower with Limberg's score ≥ 2 (AUC: 0.812)
Goodsall *et al*[4]	Prospective	19 UC (29 paired data)	NS	Milan ultrasound criteria (MUC), BWT, CDI, BWS	NHI	Coefficient: 0.14, $P = 0.011$; MUC > 6.3 and/or FCP ≥ 100 μg/g for NHI > 1 sensitivity 88%, specificity 90%, PPV 95%, NPV 57%

PPV: Positive predictive value; NPV: Negative predictive value; UC: Ulcerative Colitis; CD: Crohn' disease; CDI: Color Doppler intensity; BWT: Bowel wall thickness; AUC: Area under the curve; NHI: Nancy histologic index; BWS: Bowel wall stratification; IUS: Intestinal ultrasound.

Table 11 Summary of studies on intestinal ultrasound in pediatric inflammatory bowel disease

Ref.	Study type	Number of patients	Follow-up duration	Gold standard	Comparator	Results
Borthne *et al*[48]	Prospective	43 children with suspected IBD	3 wk	Endoscopy	Endoscopy	Sensitivity and accuracy of IUS compared to endoscopy: 93.3%
Bremner *et al*[49]	Prospective	12 UC (25 CD, 1 indeterminate colitis, 6 normal)	Cross-sectional	ileo-colonoscopy	Ileo-colonoscopy	Colonic BWT > 2.9: Sensitivity for moderate/severe disease: 48%, specificity: 93%, PPV: 83%; ileal BWT > 2.5 mm: Sensitivity for moderate/severe disease: 75%, specificity: 92%, PPV: 88%
Haber *et al*[47]	Prospective	21 UC pediatrics (26 CD, controls)	Cross-sectional	Ileo-colonoscopy	Ileo-colonoscopy	Sensitivity and specificity of IUS as compared to endoscopy: 77% and 83%, respectively
Ziech *et al*[8]	Prospective	28 suspected IBD pediatrics	Cross-sectional	Ileocolonoscopy and endoscopy	MR colonography	Sensitivity IUS: 55%; MR colonography: 57%. Specificity IUS: 100%; MR colonography: 75%; cannot effectively differentiate UC and CD unless terminal ileum is involved
Barber *et al*[71]	Retrospective	53 children	Cross-sectional	Combined consensus score based imaging and clinical scores	MRE	Clinical correlation of IUS score (0.657) > MRE score (0.598); agreement for IUS scoring: Coefficient 0.95
Chavannes *et al* [72]	Cross-sectional, single centre	33 children with suspected IBD (1 UC)	Cross-sectional	Ileo-colonoscopy	Ileo-colonoscopy	Colonic BWT > 1.9 mm: AUC 0.743, sensitivity: 64%. specificity: 76% to detect inflamed bowel. Agreement with colonoscopy: Prediction of IBD: 69.7%, kappa = 0.52; distribution of disease: 45.5%, kappa = 0.48
Dell'Era *et al*[7]	Retrospective	113 suspected pediatric IBD	1 year	Ileo-colonoscopy and 1 year follow-up	Ileo-colonoscopy	IUS bowel pattern, mesenteric hypertrophy, and BWT > 3; all 3 sensitivity: 57.5%; specificity: 100%
Scarallo *et al*[35]	Single centre, retrospective	25 acute severe UC patients	Cross-sectional	NA	PUCAI > 45 at day 3; PUCAI > 65 day 5	At day 3 BWT > 3.4 mm and loss of BWS are independent predictors of steroid failure; BWT > 3.4 mm 92% sensitivity and 52% specificity for steroid resistance; PUCAI > 45 at day 3: 80.6% sensitivity and 45.5% specificity; PUCAI > 65 at day 5: 33.3% sensitivity and 90% specificity
van Wassenaer *et al*[68]	Prospective cross-sectional	22 UC	Cross-sectional	Ileo-colonoscopy	Physicians *vs* radiologists	Moderate inter-observer agreement for disease activity in terminal ileum (kappa = 0.58), descending colon (kappa = 0.52), and transverse colon (kappa = 0.49) between radiologists (AUC: 0.67-0.79) and gastroenterologists (AUC: 0.71-0.81)
Hudson *et al*[69]	Cross-sectional study	35 CD,15 UC,4 IBD	Cross-sectional	SES-CD, Mayo endoscopic score	MRE and endoscopy	High patient and caregiver satisfaction. Preferred over MRE and colonoscopy. No concern about IUS findings in those with co-existing anxiety
van Wassenaer *et al*[64]	Prospective cross-sectional	35 UC (pediatric)	Cross-sectional	Mayo endoscopic score	Endoscopy	UC-IUS score better than Civitelli index for both sensitivity (88-100% *vs* 65%-80%) and specificity (84%-87% *vs* 89%-93%) (MES ≥ 2); higher AUC in ascending colon (0.82 *vs* 0.76) and transverse colon (0.88 *vs* 0.77). No difference in descending colon (both 0.84)
Mohamed *et al* [74]	Prospective	40 IBD	Cross-sectional	Clinical and fecal calprotectin	Clinical activity	Combined gray scale ultrasound, color Doppler, and shear wave elastography increase accuracy (92%) with 100% accuracy
Otani *et al*[73]	Retrospective	40 UC	Cross-sectional	Colonoscopy and fecal calprotectin	Fecal calprotectin	Accuracy of sum of adjusted bowel wall thickness was higher than fecal calprotectin for detecting moderate colonic inflammation (Mayo endoscopic score 2)
Spyropoulou *et al* [70]	Prospective	32 UC	cross-sectional	Colonoscopy	Colon capsule endoscopy, fecal calprotectin	Sensitivity, specificity, PPV, and NPV of US are 85%, 92%, 94%, and 79%, respectively. Noninvasive approach combining CCE, FCP, and IUS better tolerated than colonoscopic monitoring

CD: Crohn's disease; UC: Ulcerative colitis; TI: Terminal ileum; IUS: Intestinal ultrasound; HRUS: High resolution ultrasound; MRI: Magnetic resonance imaging; MRE: Magnetic resonance enterography; BWT: Bowel wall thickness; PCD: Pediatric Crohn's disease; UC-IUS: Ulcerative colitis intestinal ultrasound score; PCDAI: Paediatric Crohn Disease Activity; CCE: Colon capsule endoscopy; FCP: Fecal calprotectin; AUC: Area under curve; IBD: Inflammatory bowel disease; PUCAI: Pediatric ulcerative colitis activity index, PPV: Positive predictive value; NPV: Negative predictive value.

substantial for both new (kappa = 0.64) diagnosis and relapsing (kappa = 0.63) cohort. Agreement for colonic disease in new and relapsed diseases was fair (kappa = 0.27) and moderate (kappa = 0.56), respectively[87].

So overall, IOA is substantial for several IUS parameters with the highest agreement for BWT which varies by region of the bowel involved. The agreement may be higher for colonic involvement in established disease over new diagnosis.

Point-of-care IUS and clinical decision-making: POCUS has been shown to influence real-time management of IBD in several studies, impacting management in 40%-60%of cases[86,88]. Clinically inactive disease can have activity detectable by IUS. The impact on management varied from escalation/de-escalation of therapy and making surgical decisions[60]. POCUS has moderate agreement with MRE and ileo-colonoscopy. POCUS has a good correlation with MRE and also colonoscopy in detecting the presence, extent, and complications of the disease in CD and UC (Table 13)[80].

Clinical decision-making based on IUS has been shown to effectively treat inflammation based on follow-up of the patients in a retrospective cohort study in the United States (108 CD; 39 UC, 14 active disease, 25 in remission)[89]. IUS plays an important role in therapeutic optimization. A prospective study including both UC and CD patients (89 UC, 28 CD) showed that BWT and CDS intensity independently predicted immediate therapeutic intensification whereas loss of bowel wall stratification along with BWT predicted subsequent therapeutic optimization[29]. A similar study during the COVID-19 pandemic (123 CD, 18 UC) showed that clinical assessment with IUS resulted in an acute management change in 57% of cases and avoiding/delaying colonoscopy in 85%[90].

Utility of IUS

Patient acceptability: Patient acceptability is one of the unique aspects of IUS. The acceptability of IUS, MRE, and colonoscopy was 99%, 88%, and 60%, respectively. However, patients emphasized that test accuracy is more important than discomfort[91]. Similarly, another international study with 37 participants revealed that noninvasive monitoring strategies like IUS were preferred although they were willing for invasive modalities like colonoscopy if warranted. They stressed the importance of patient involvement in shared decision-making[92]. For pediatric patients, both patients and caregivers preferred IUS over other modalities and found it more informative to understand their disease[69].

Cost-effectiveness: Although IUS seems to be cost-effective over other modalities of monitoring, it has not been studied extensively. A cost-effectiveness study performed in the United Kingdom showed that up to 55% of MREs and 28% of colonoscopies/sigmoidoscopies could be avoided by the introduction of IUS. The potential lesions to be missed were colonic polyps (n = 2) seen on colonoscopy and upper GI/extra-intestinal manifestations (EIM) in MRE. However, there was no upper GI involvement and the EIMs were of limited significance. The projected annual cost savings was £ 500000 [93]. As compared to MRE, the cost (5 times lower) and scheduling time (2 times shorter) for IUS are significantly lower based on a retrospective survey in the United Kingdom[94]. It is important to recognize that cost-effectiveness and billing strategies differ in several parts of the world.

Survey on widespread adoption of IUS: Three studies from the United Kingdom performed at different timelines have shown that IUS is increasingly being adopted but still, there is a need for expansion. In the first study published in 2014, IUS was performed only for younger patients (< 40 years) with low suspicion of CD in 44% of radiology departments[95].

Table 12 Summary of studies on transperianal ultrasound in ulcerative colitis

Ref.	Study type	Number of patients	Follow-up duration	Comparator	USG parameters	Results
Sagami *et al*[57]	Cross-sectional	55 UC	Cross-sectional	Endoscopy, Histopathology	BWT, CDS, BWS	BWT ≤ 4 MM predicts endoscopic healing (MES ≤ 1), AUC = 0.904. BWT ≤ 4 MM predicts rectal histologic mucosal healing, AUC = 0.869. Better than FCP
Sagami *et al*[78]	Prospective, single centre	100 UC	Cross-sectional	FCP, CRP	BWT, CDS	Rectal ΔBWT at 1 wk predicted remission at 8 wk (odds ratio for 1 mm increase is 1.9); FCP did not predict remission

MES: Mayo endoscopic score; UC: Ulcerative colitis; FCP: Fecal calprotectin; CRP: C- reactive protein; BWT: Bowel wall thickness; CDS: Color Doppler signal; AUC: Area under the curve; BWS: Bowel wall stratification.

Table 13 Summary of studies evaluating role of point-of-care ultrasound in inflammatory bowel disease

Ref.	Study type	Comparator	Follow-up duration	Number of patients	Impact on management
Bots *et al*[60]	Retrospective	MRI, colonoscopy	MRE within 8 wk of IUS	345 (280 CD and 65 UC)	POCUS changed management in 60%; change in medications 48%; correlation with IUS 86.3%; correlation with MRI 80%; reduced use of MRI with increased adoption of IUS
Sathananthan *et al*[58]	Prospective	Ileocolonoscopy	POCUS & ileocolonocscopy within 30 d of one another	74 (CD 35; UC 39)	Correlation with same day colonoscopy (sensitivity 100%, specificity 100%, PPV 100%, NPV 100%, kappa 1); correlation with colonoscopy within 30 d (sensitivity 92%, specificity 86%, PPV 92%, NPV 86%, kappa 0.77 (MES ≥ 1); extent: Sensitivity 92%, specificity 80%, PPV 88%, NPV 86%, kappa 0.7
Carter *et al*[53]	Retrospective	MRE	Cross-sectional	11 UC (167 CD)	Sensitivity 90%; specificity: 23% as compared to colonoscopy/MRE (combined CD and UC); impact on management not evaluated
de Voogd *et al* [2]	Prospective, single centre cohort	Clinical activity and FCP	Prospective, single centre cohort study	16 UC, 22 CD	Impact on management (56.25%); treatment escalation: *n* = 6 (UC); continue same treatment: *n* = 3 (UC)
Saleh *et al*[89]	Retrospective	Clinical (UCAI ≤ 5 and partial Mayo ≤ 2) and biomarker remission (ESR ≤ 40 mm/h and CRP ≤ 10 mg/L and fecal calprotectin ≤ 50 μg/mg and fecal lactoferrin ≤ 30 μg/mL)	Mean time between follow-up IUS 203 d	39 UC, 108 CD	25 active UC on IUS; change in plan: 13; continue therapy: 11; deescalate therapy: 1; 14 inactive UC; 80.7% continued therapy (overall IBD); 5.2% deescalated therapy; 14% change in therapy Treatment change more in those with higher BWT (≥ 5 mm, < 5 mm-> 3 mm, ≤ 3 mm); Treatment change did not differ by CDS (Limberg's score 0, 1, ≥ 2)
Lu *et al*[77]	Prospective, observational	Sigmoidoscopy, FCP, CTE/MRE	1 year	UC-16 (CD-46)	Change in management in 80% with IUS only (all IBD); Sigmoidoscopy + IUS 83% change in management

CD: Crohn's disease; MRE: Magnetic resonance enterography; IUS: Intestinal ultrasound; UC: Ulcerative colitis; MRI: Magnetic resonance imaging; BWT: Bowel wall thickness; POCUS: Point-of-care intestinal ultrasound; HHIUS: Hand-held intestinal ultrasound.

An Italian study showed that 24% of ultrasound referrals were for bowels with equal distribution of suspected and confirmed GI diseases[96]. A recent survey showed that 30% had IUS service (100% had MRI service) with a shorter average reporting time (1-4 wk) (MRI 4-6 wk)[97]. A survey of stakeholders (*n* = 14) identified perceived barriers and benefits of the implementation of IUS services (Table 14)[98]. A survey in Australia among 121 IBD patients showed that IUS was the preferred monitoring tool which improved IBD-specific knowledge[99]. In a Dutch retrospective cohort study, the use of POCUS increased over time for IBD monitoring along with the decline in the use of MRI[60].

DISCUSSION

The systematic scoping review highlights the role of IUS from diagnosis in suspected IBD/UC to monitoring and prediction tools in known UC. We have summarized the current evidence behind each indication of IUS and highlighted

Table 14 Summary of studies on implementation of intestinal ultrasound services

Ref.	Year	Country	Survey participants	Main results
Maconi *et al* [96]	2011	Italy	12 sonographers	24% of ultrasound referrals were for bowel ultrasound; 78% referred by gastroenterologists; half for suspected bowel disease and half for follow-up
Hafeez *et al* [95]	2014	United Kingdom	63 radiology and 73 gastroenterology departments	Barium meal follow through and CT preferred for luminal and extraluminal complications; IUS mainly for young patients with low suspicion of Crohn's disease; used in 44% of radiology departments
Rajagopalan *et al*[99]	2019	Australia	121 patients	IUS scored highest in the visual analogue scale as compared to colonoscopy, stool/blood sampling/imaging; IUS improved patient IBD specific knowledge of the need for medical therapy and disease extent
Radford *et al* [97]	2022	United Kingdom	103 IBD physicians	30% have IUS service (100% had MRI service); average time to reporting; USG (1-4 wk) (MRI: 4-6 wk); 59.6% confident in clinical decision-making using USG (MRI: 97%)
Radford *et al* [98]	2023	United Kingdom	14 stakeholders	Barriers to implement IUS service: (1) Reliance on existing imaging pathways; (2) Reluctance to change; (3) Perceived lack of precision; and (4) Initial financial and time outlay. Perceived benefits: (1) Reduced waiting time; (2) Earlier diagnosis and treatment allocation; (3) Reduced hospital appointments; and (4) Better understanding of disease

CT: Computed tomography; USG: Ultrasonography; IBD: Inflammatory bowel disease; MRI: Magnetic resonance imaging; IUS: Intestinal ultrasound.

the unmet needs and shortcomings of existing evidence.

Prospective studies indicate that IUS is a valuable diagnostic tool for suspected IBD and UC, particularly in patients with low-risk gastrointestinal symptoms where it helps to exclude irritable bowel syndrome. The sensitivity, specificity, PPV, and NPV of IUS in suspected IBD vary, with sensitivity ranging between 55%-85% and specificity between 95%-100%. Sensitivity is higher for diagnosing CD (84%) compared to UC (38%-66%), and higher for ileal (92%-96%) and left colonic lesions (81%-87%) compared to duodenal/jejunal (29%-33%) and rectal lesions (14%-15%). The loss of stratification among IUS parameters has the highest sensitivity (78.3%), and combining parameters improves diagnostic accuracy. Despite its promise, IUS has limitations, particularly in differentiating UC from its mimics, and more studies are needed to standardize its application, improve its sensitivity, especially in challenging anatomical areas, and validate its use in different clinical scenarios[1,3].

Assessing disease activity in IBD using IUS involves several parameters, with BWT and CDS intensity being the most reliable indicators according to an IOA study among expert sonographers[15]. Various scoring systems, such as the MUC and UC-IUS index, have been developed and validated to correlate IUS findings with endoscopic activity. The Milan criteria uses BWT and CDS to predict endoscopic activity with high accuracy, and its predictive value is enhanced when combined with FCP. MUC has shown efficacy in predicting adverse outcomes and endoscopic remission in UC patients. The UC-IUS index incorporates BWT, CDS intensity, lack of haustrations, and fat wrapping, demonstrating an excellent correlation with endoscopic scores and substantial inter- and intra-rater agreement[17]. IUS parameters with or without FCP can even predict histologic response[2,4]. The KUC, which use BWT and SMT, provide a high PPV for endoscopic improvement, highlighting the utility of IUS in non-invasive disease monitoring and management. Although several such scoring systems have been developed for UC and pediatric IBD, only a few are validated (*e.g.*, MUC) for treatment response and outcome prediction[4].

Monitoring therapeutic response and disease course in UC using IUS has demonstrated significant utility across various studies. The short-term goal of UC management focuses on clinical response, with intermediate and long-term goals targeting the normalization of biomarkers and mucosal healing, including histologic healing. Recent research, such as the TRUST UC study, confirmed that IUS parameters like BWT could predict clinical flare and treatment response, with normalization preceding clinical and biomarker improvements[28]. Prospective studies have reinforced the role of IUS in predicting treatment escalation and monitoring therapeutic responses over various timeframes. For instance, the IUS response to therapy can be detected as early as 2 wk even before clinical and biochemical response[28]. The timeline for assessing therapeutic response is drug-dependent, *i.e.*, response to Janus Kinase inhibitors and steroids can often be assessed by IUS within days; however, other medications would be recommended to be reassessed at a longer interval [33]. Additionally, IUS is a reliable surrogate for endoscopic outcomes, with specific criteria like the MUC effectively predicting disease severity, corticosteroid failure, and the need for colectomy. In acute severe UC, IUS parameters such as a > 20% reduction in BWT soon after initiating IV steroids were predictive of clinical response and the necessity for rescue therapy, underscoring the importance of IUS in acute settings[35]. Overall, IUS emerges as a valuable, non-invasive tool for monitoring disease activity, therapeutic response, and predicting long-term outcomes in UC. POCUS can alter the management of IBD in 40%-60% of cases although more data is required to support a "treat to target strategy" based on POCUS[86].

The correlation of IUS with other diagnostic modalities in UC demonstrates its potential as a comprehensive non-invasive tool for disease assessment. Several studies have highlighted the strong association between IUS parameters, such as BWT and CDS, with clinical indices, biomarkers like FCP and CRP, and histological activity. IUS correlates well with colonoscopy findings, with BWT showing consistent accuracy in reflecting endoscopic severity scores such as the MES and UCEIS. The MUC and UC-IUS scores further enhance the predictive capability of IUS, with studies indicating significant agreement with endoscopic assessments and histological grades[4]. IUS correlates well with ileo-colonoscopy except in the rectum. Trans-perineal and trans-vaginal ultrasound have shown promise in evaluating rectal involvement

in UC, offering high accuracy in predicting endoscopic and histological healing[57]. Additionally, IUS demonstrates comparability with MRE in evaluating large bowel inflammation, though differentiation between UC and CD remains challenging without ileal involvement[56]. The ability of IUS to monitor TH provides a valuable therapeutic target, supporting its integration into routine clinical practice for managing UC. Overall, these findings underscore the utility of IUS in providing a reliable, non-invasive alternative for comprehensive disease monitoring and therapeutic response evaluation in UC patients[32]. More evidence is required to conclusively prove that change in decision-making based on IUS improved clinical outcomes.

IUS is proving to be a versatile and effective tool in managing UC across special populations, including pediatric patients, pregnant women, and during the COVID-19 pandemic. In children, IUS offers a non-invasive alternative to colonoscopy and MRI, showing high accuracy in assessing disease location and severity with a favorable patient experience. Studies indicate that IUS can predict steroid responsiveness and provide valuable insights into disease activity and histological severity, often correlating well with biomarkers such as FCP. Pediatric IUS scores need to be validated further with age-specific cut-offs. For pregnant women, IUS serves as a safe, radiation-free method to monitor IBD, although its feasibility decreases in the third trimester as a gravid uterus can hinder the evaluation of the sigmoid colon and terminal ileum[75]. During the COVID-19 pandemic, IUS facilitated changes in clinical management and reduced the need for endoscopic procedures, highlighting its role in urgent care settings. These findings underscore the growing utility of IUS as a non-invasive, effective diagnostic and monitoring tool across diverse patient groups and clinical scenarios.

The utility of IUS in managing IBD/UC is multifaceted, with high patient acceptability, potential cost-effectiveness, and growing adoption in clinical practice. Patients overwhelmingly prefer IUS due to its non-invasive nature, despite valuing test accuracy over comfort, with pediatric patients and caregivers also favoring it for its informativeness[69]. Cost-effectiveness studies suggest significant savings by reducing the need for MRE and colonoscopies, although these findings need broader validation[93]. Surveys indicate that while IUS adoption is increasing, with shorter scheduling and reporting times compared to MRI, there remain barriers to its widespread implementation. Barriers to the implementation of gastroenterologist-led ultrasound were a lack of widespread training programs, increased workload, and protectionist behavior from the radiologist[83]. Hand-held IUS can help in the widespread dissemination of IUS and was shown to be as good as conventional IUS[22]. Studies underscore the necessity for patient involvement in decision-making, and research highlights a preference for IUS, reflecting its growing role in routine IBD monitoring and its capacity to enhance patient knowledge and reduce reliance on more invasive procedures.

CONCLUSION

IUS is an emerging, non-invasive, radiation-free, highly sensitive, and dynamic tool for monitoring UC. Current indications include diagnosis of IBD, assessment of disease activity/complications, and monitoring and prediction of therapeutic response or clinical outcomes in UC. IUS can predict endoscopic response and even histologic healing in UC. IUS parameters can predict response to biologics and small molecules as early as 2 wk. IUS has the potential to replace MRE and ileo-colonoscopy given its high accuracy, except for upper GI, jejunal, and rectal lesions, and surveillance of colitis-associated neoplasia. IUS is also helpful in special situations such as pregnancy and pediatric UC. IUS by trained gastroenterologists is as accurate as that by radiologists. POCUS alters management in a substantial number of patients although comparative studies with standard management for the “treat to target” strategy are lacking.

Future research should focus on the long-term outcomes of IUS-based management to establish its efficacy and sustainability in routine clinical practice. Comparative studies with traditional management strategies are necessary to confirm the benefits of IUS in a "treat to target" approach. Additionally, expanding research on IUS's effectiveness in detecting upper GI, jejunal, and rectal lesions, as well as its role in the surveillance of colitis-associated neoplasia, is essential. Investigating the integration of IUS into telemedicine and remote monitoring could also broaden its accessibility and utility. Ultimately, addressing the existing knowledge gaps and gray areas will solidify IUS's position as a cornerstone in the management of UC.

FOOTNOTES

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META-ANALYSIS

Incidence and predictors of hypocalcemia in end-stage renal disease patients on denosumab therapy: A systematic review and meta-analysis

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Abstract

BACKGROUND

Denosumab inhibits the receptor activator of nuclear factor kappa-ligand. It markedly increases bone mineral density and has been proven to reduce the risk of fractures. However, numerous adverse effects, notably hypocalcemia, are prevalent in patients with end-stage renal disease (ESRD).

AIM

To analyze the incidence and predictors of hypocalcemia caused by denosumab compared to control in patients with ESRD.

METHODS

We conducted this study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. PubMed, Scopus, Cochrane Central, and EMBASE were systematically searched from inception through March 2024. All original studies investigating the effects of denosumab on patients with ESRD compared to control were extracted. The primary outcomes of our study were the incidence of mild, severe, and very severe hypocalcemia. Secondary outcomes included serum levels of intact parathyroid hormone, calcium, and phosphate. The results were pooled and analyzed using a random-effects model.

RESULTS

Seven articles comprising 3240 patients were included in our study. Patients treated with denosumab had a significantly increased incidence of mild hypocalcemia [risk ratio (RR): 2.79; 95% confidence interval (CI): 0.99-7.91; P = 0.05; I^2 = 37%] and of very severe hypocalcemia (RR: 9.58; 95%CI: 1.58-57.98; P = 0.01; I^2 = 49%). However, an increase in the occurrence of severe hypocalcemia was non-significant (RR: 4.23; 95%CI: 0.47-38.34; P = 0.20; I^2 = 96%). Alternatively, denosumab showed a significant decrease in serum intact parathyroid hormone [mean difference (MD): -433.20, 95%CI: -775.12 to -91.28, I^2 = 98%, P= 0.01], while there was a non-significant decrease in phosphate (MD: -0.47, 95%CI: -1.35 to 0.41, I^2 = 88%, P = 0.30) and calcium levels (MD: -0.33, 95%CI: -0.95 to 0.29, I^2 = 94%, P = 0.29).

CONCLUSION

Our study demonstrated that denosumab is significantly associated with mild and very severe hypocalcemia in patients with ESRD making it necessary to detect and prevent this side effect of treatment.

Key Words: Denosumab; End-stage renal disease; Hypocalcemia; Parathyroid hormone; Dialysis

Core Tip: Denosumab is a monoclonal antibody that inhibits receptor activator of nuclear factor kappa-B-ligand and prevents bone resorption, making it useful for treating osteoporosis. Although denosumab has an acceptable safety profile, it is known to cause hypocalcemia in patients with renal insufficiency making it contraindicated in patients with hypocalcemia. Such patients may experience muscle and joint pain. To date, very few randomized controlled trials have explored the safety of this drug in patients with end-stage renal disease or on dialysis. This meta-analysis thus appraised the safety profile of denosumab in patients with end-stage renal disease.

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INTRODUCTION

Osteoporosis is characterized by brittle bones, which are susceptible to fracture owing to low bone mineral density. This condition is more common in older adults, especially postmenopausal women, and develops progressively over the years [1]. Genetic factors, hormonal fluctuations, certain medications such as chronic corticosteroid use, low levels of calcium and vitamin D, and a sedentary lifestyle are contributory factors[1-3].

End-stage renal disease (ESRD), the advanced form of chronic kidney disease (CKD), is also associated with an increased risk of fragility fractures. ESRD is indicated by an estimated glomerular filtration rate (eGFR) of less than 15 mL/min[4-6]. Osteoporosis is considered a significant complication of CKD[4,5]. Abnormalities in mineral metabolism emerge from impaired kidney function in ESRD, resulting in elevated phosphate and decreased calcium levels[6].

In order to mitigate osteoporosis secondary to ESRD, denosumab, an inhibitor of receptor activator of nuclear factor kappa-B-ligand, is useful in increasing bone mineral density and reducing the risk of fractures in patients with ESRD[7]. Changes to calcium and phosphate levels in these patients can be hindered by preexisting abnormalities in mineral metabolism as a complication of ESRD. This can be further explained by the high incidence of hypocalcemia in patients receiving denosumab for ESRD and CKD treatment[8]. Hypocalcemia can precipitate symptoms including muscle spasms, peripheral numbness, disorientation, forgetfulness, swallowing difficulties, irregular heart rhythm, brittle nails, hair thinning, and decreased bone density leading to osteoporosis[9-11].

The use of denosumab in ESRD patients and its adverse effects such as hypocalcemia have not been established in the existing literature with conflicting evidence being reported by published studies. Therefore, we conducted this meta-analysis to evaluate the safety of denosumab treatment and the associated risk for hypocalcemia in patients with ESRD with recently published large-scale studies to aid clinicians in prescribing denosumab to patients with ESRD.

MATERIALS AND METHODS

This review was conducted in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses [12].

Search strategy

An extensive search of PubMed, Scopus, EMBASE, and Cochrane Library was conducted from inception through March 2024. There were no limitations regarding language, location, author, year of publication, or any other aspect. The terms applied for the search were: (1) Denosumab; (2) Hypocalcemia; (3) Dialysis; (4) End stage renal disease; and (5) ESRD. A more detailed search strategy is given in Supplementary Table 1. Moreover, to identify grey literature, ClinicalTrials.gov, Medrxiv.org, and Google Scholar were searched. Additionally, we carried out a comprehensive review of the references cited in our study to acquire relevant articles.

Study selection

Two independent investigators (Fahim MAA and Salman A) screened the titles and abstracts of the articles that remained after duplicate removal through the EndNote Reference library (Version X7.5; Clarivate Analytics, Philadelphia, PA, United States), with a full-text review conducted to determine their relevance. After this, a third reviewer (Siddiqui AH) was sought to resolve any discrepancies. Additionally, the reference lists of included articles were manually examined to identify relevant studies.

Inclusion and exclusion criteria

The eligibility criteria for studies included were: (1) Population: Adults > 18 years of age with ESRD (eGFR < 15 mL/min) or on dialysis; (2) Intervention: Denosumab; (3) Control: Any; and (4) Outcomes: Any of our primary or secondary outcomes. Conference abstracts, letters, case reports, and studies containing inadequate original data for further analysis comprised our exclusion criteria.

Study outcomes

Our primary outcomes were incidence of mild (< 8.0 mg/dL), severe (< 7.5 mg/dL), and very severe (< 6.5 mg/dL) hypocalcemia. Our secondary outcomes consisted of changes in calcium level (mg/dL), changes in phosphate level (mg/dL), and changes in intact parathyroid hormone (iPTH) levels (pg/mL).

Data synthesis and analysis

Published data was analyzed using RevMan (version 5.4.1; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020), and the results were pooled as risk ratio (RR) or mean differences (MD) with their respective 95% confidence interval (CI). Comprehensive Meta Analyst (version 3.7) was used for all meta-regression analyses. All the outcomes were analyzed using the random effects model owing to the diversity of articles included. The significance of the results obtained was authenticated *via* a forest plot. A *P* value lower than 0.05 was considered significant. Heterogeneity across the pooled studies was examined using the Higgins I^2 statistics. A value of I^2 = 25%-50% was considered mild, I^2 = 50%-75% was moderate, and I^2 > 75% was significant heterogeneity. A sensitivity analysis was conducted for all results that presented significant heterogeneity.

Data extraction

Study and baseline characteristics were extracted onto an Excel sheet and verified by two authors (Fahim MAA and Salman A) with a third author (Siddiqui AH) being consulted on disagreement. Data from all studies included was extracted and organized according to author name, year of publication, study design, population type and size, denosumab dosage and route of administration, control drug and dosage, outcomes of each study, follow-up duration, general patient characteristics (age, sex, and body mass index), diabetes mellitus, baseline serum calcium (mg/dL), phosphate (mg/dL), 25-hydroxyvitamin D (ng/dL), iPTH (pg/mL), and alkaline phosphatase (IU/L) values, use of vitamin D analogues, and primary and secondary endpoints. Additionally, data was interconverted from medians to means and from various other units to the aforementioned units.

Quality assessment

The Cochrane Collaboration Risk of Bias Tool 2.0 was used to evaluate the quality of the included randomized clinical trials[13]. The Cochrane Collaboration Risk of Bias Tool 1.0 was used for the evaluation of non-randomized open-label clinical trials[14]. The Newcastle Ottawa Scale was used to assess bias in the included retrospective observational cohort studies[15] with the Newcastle Ottawa Scale assessment for case-control studies being used for the quality assessment of case controls[15]. Lastly, the National Institute of Health tool was used to assess the quality of the case series[16].

RESULTS

The search initially retrieved 202 records from databases from which seven studies involving 1793 patients with ESRD or on dialysis and osteoporosis being treated with denosumab were finally included. A more detailed overview of the process is presented in Figure 1. These patients were compared with control groups constituting a number of 1447 patients. Among these studies, two were observational retrospective cohort studies[17,18], one was a case series[19], one was a case-control study[20], two were open-label clinical trial studies[21,22], and one was a randomized controlled trial [23]. The characteristics of the included studies are summarized in Table 1 with baseline characteristics included in Table 2.

Table 1 Study characteristics

Ref.	Study design	Study sample	Sample size		Denosumab route of administration	Denosumab dosage	Control drug and dosage	Outcomes	Follow-up duration
			Denosumab	Control					
Bird *et al* [17], 2024	Observational retrospective cohort study	Dialysis-dependent Medicare postmenopausal female patients aged ≥ 65 years	1523	1281	Subcutaneous	60 mg (6 monthly)	Oral bisphosphonate (alendronate, risedronate, and ibandronate) 70 mg (weekly)	Severe hypocalcemia (albumin-corrected serum calcium levels < 1.88 mmol/L, primary hospital hypocalcemia diagnosis, or emergency department hypocalcemia diagnosis); Very severe hypocalcemia (serum calcium levels < 1.63 mmol/L or emergency care)	12 wk
Cowan *et al*[18], 2023	Observational retrospective cohort study	Adults aged > 65 years with a new drug prescription for oral bisphosphonate or denosumab on chronic dialysis or eGFR < 15 mL/min/1.73 m^2	174	85	Subcutaneous	60 mg (6 monthly)	Oral bisphosphonate (etidronate, alendronate, and risedronate)	Mild hypocalcemia (albumin-corrected serum calcium or levels < 2.0 mmol/L or ionized calcium levels < 1.0 mmol/L) within 180 d of new oral bisphosphonate/denosumab prescription; Severe hypocalcemia (albumin-corrected serum calcium or levels < 1.8 mmol/L or ionized calcium levels < 0.9 mmol/L) within 180 d of new oral bisphosphonate/denosumab prescription	180 d
Chen *et al*[19], 2020	Observational single-center case series	Patients with ESRD with SHPT and low bone mass undergoing dialysis	21	21	Subcutaneous	60 mg (single dose)	Conventional treatment	Changes in calcium, phosphate, and ALP levels; Changes in CAC from baseline; Adverse events	6 mo
Iseri *et al* [23], 2019	Randomized controlled trial	Patients diagnosed with osteoporosis undergoing hemodialysis	22	24	Subcutaneous	60 mg (6 monthly)	IV alendronate 900 mg (every 4 wk for 1 year)	Changes from baseline to 12 mo in LSBMD, BMD at other sites; Changes from pretreatment to 12 mo in BTM; Changes in serum calcium and phosphate levels from day 0 to day 14; New fractures and adverse events	12 mo
Takami *et al*[20], 2017	Observational retrospective case-control study	Patients with low BMD (< 70% of the young adult mean) undergoing hemodialysis	17	20	Subcutaneous	60 mg (6 monthly)	No denosumab	Changes in phosphorus, calcium, whole PTH, total ALP, and albumin levels from baseline to 12 mo; Radius BMD	12 mo
Chen *et al*[21], 2015	Open-label clinical trial	Patients with SHPT and low bone mass undergoing dialysis	24	8	Subcutaneous	60 mg (single dose)	No denosumab	Parathyroid gland volume; BMD; Adverse outcomes; Changes in serum calcium, phosphate, ALP, and iPTH from baseline to study completion	24 wk
Chen *et al*[22], 2014	Open-label clinical trial	Patients with ESRD and severe SHPT undergoing dialysis	12	8	Subcutaneous	60 mg (single dose)	No denosumab	Changes in serum calcium, phosphorus, ALP, BMD, and iPTH levels	6 mo

ALP: Alkaline phosphatase; BMD: Bone mineral density; BTM: Bone turnover marker; CAC: Coronary artery calcification; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; iPTH: Intact parathyroid hormone; IV: Intravenous; LSBMD: Lumbar spine bone mineral density; PTH: Parathyroid hormone; SHPT: Secondary hyperparathyroidism.

Quality assessment

In the included studies all randomized and non-randomized controlled trials were revealed to have a low risk of bias. Additionally, all cohort and case-control studies included in the analysis were also revealed to have a low risk of bias as they achieved scores of eight. Moreover, all case series received a quality rating of 'Good.' A detailed summary of quality assessment is presented in Supplementary Figures 1 and 2, Supplementary Tables 2-4.

Table 2 Baseline characteristics

Characteristic	Subcategory	Bird *et al* [17], 2024	Cowan *et al* [18], 2023	Chen *et al* [19], 2020	Iseri *et al* [23], 2019	Takami *et al* [20], 2017	Chen *et al* [21], 2015	Chen *et al* [22], 2014
Sample size	Denosumab	1523	174	21	22	17	24	12
	Control	1281	85	21	24	20	8	8
Female/male	Denosumab	1523/0	141/33	18/3	9/13	0/17	19/5	5/7
	Control	1281/0	48/37	12/9	9/15	0/20	2/6	3/5
Age in yr	Denosumab	74.5 ± 6.6	79.2 ± 7.7	62.14 ± 2.50	71.3 ± 10.5	72.8 ± 9.5	58.38 ± 2.77	53.5 ± 3.8
	Control	73.8 ± 6.5	78.0 ± 7.3	54.76 ± 2.00	71.5 ± 9.3	71.2 ± 11.0	58.50 ± 2.38	N/A
Serum calcium in mg/dL	Denosumab	9.3 ± 0.5	9.48 ± 0.16	9.96 ± 0.20	9.2 ± 0.5	9.2 ± 0.5	10.08 ± 0.16	10.1 ± 0.4
	Control	9.2 ± 0.6	9.4 ± 0.19	9.73 ± 0.20	9.3 ± 0.3	9.0 ± 0.5	10.30 ± 0.37	10.1 ± 0.3
Serum phosphate in mg/dL	Denosumab	4.7 ± 1.0	14.353 ± 0.67	5.50 ± 0.32	4.9 ± 1.1	5.0 ± 1.3	5.68 ± 0.29	5.3 ± 0.3
	Control	4.7 ± 1.1	14.477 ± 0.65	5.69 ± 0.21	4.6 ± 1.2	4.8 ± 1.2	5.79 ± 0.34	6.0 ± 0.3
Serum 25(OH)D in ng/mL	Denosumab	N/A	29.22 ± 12.34	27.01 ± 2.29	22.5 ± 9.5	N/A	30.04 ± 3.08	N/A
	Control	N/A	31.18 ± 14.05	25.16 ± 2.54	18.0 ± 9.3	N/A	32.36 ± 5.68	N/A
iPTH in pg/mL	Denosumab	N/A	295 ± 319.9	1310.50 ± 108.40	127.5 ± 83.2	150.2 ± 137.02	1464.77 ± 93.17	1702.1 ± 181.9
	Control	N/A	345.5 ± 456.81	1044.74 ± 61.24	138.4 ± 88.6	165.33 ± 98.14	974.58 ± 53.76	1300.1 ± 132.1
ALP in IU/L	Denosumab	N/A	N/A	268.38 ± 30.43	244.6 ± 60.8	276 ± 129	331.67 ± 48.86	449.8 ± 94.2
	Control	N/A	N/A	119.86 ± 8.85	265.9 ± 145.0	270 ± 69	112.50 ± 12.37	330.1 ± 81.3
BMI in kg/m^2, mean ± SD	Denosumab	N/A	N/A	N/A	20.5 ± 2.7	21.6 ± 2.3	53.77 ± 1.74	N/A
	Control	N/A	N/A	N/A	21.1 ± 5.3	20.8 ± 2.3	62.48 ± 3.27	N/A
Diabetes	Denosumab	N/A	111 (63.8)	3 (14.3)	9 (40.9)	9 (52.9)	N/A	N/A
	Control	N/A	40 (47.1)	2 (9.5)	11 (45.8)	11 (55.0)	N/A	N/A
Use of vitamin D analogue	Denosumab	946 (62.1)	54 (31.0)	N/A	20 (90.9)	N/A	N/A	12 (100)
	Control	850 (66.4)	23 (27.1)	N/A	19 (79.2)	N/A	N/A	8 (100)

Data are presented as *n* (%) or mean ± standard deviation. 25(OH)D: 25-hydroxyvitamin D; ALP: Alkaline phosphatase; BMI: Body mass index; iPTH: Intact parathyroid hormone; N/A: Not applicable.

Primary outcomes

Six studies reported mild hypocalcemia in patients with ESRD post-denosumab administration. Overall, the analysis suggests that there is a statistically significant association and a higher likelihood of developing mild hypocalcemia after denosumab therapy when compared to the control group (RR: 2.79; 95%CI: 0.99-7.91; P = 0.05; I^2 = 37%). Six studies reported severe hypocalcemia in patients with ESRD post-denosumab administration. The analysis suggests that there is no significant difference in the occurrence of severe hypocalcemia between denosumab and control groups with high inter-study heterogeneity (RR: 4.23; 95%CI: 0.47-38.34; P = 0.20; I^2 = 96%). Three studies reported severe hypocalcemia in patients with ESRD post-denosumab administration. The analysis indicated that denosumab is associated with a significantly higher likelihood of very severe hypocalcemia compared to the control group. (RR: 9.58; 95%CI: 1.58- to 57.98; P = 0.01; I^2 = 49%) Forest plots for primary outcomes are given in Figure 2.

Secondary outcomes

Three studies were evaluated to assess the changes in serum calcium levels after denosumab treatment in patients with ESRD showing a non-significant decrease in serum calcium levels when compared to the control group. (MD: -0.33; 95%CI: -0.95 to 0.29; P = 0.29; I^2 = 94%). Three studies reported changes in iPTH levels. The pooled analysis indicated that the iPTH levels decreased significantly in patients after denosumab use, however there was high inter-study heterogeneity (MD: -433.20; 95%CI: -775.12 to -91.28; P = 0.01; I^2 = 98%). Three research studies documented alterations in phosphate levels throughout denosumab therapy. The overall effect indicated no significant difference in serum phosphate levels between denosumab and control groups with high inter-study heterogeneity (MD: -0.47; 95%CI: -1.35 to 0.41; P = 0.30; I^2 = 88%). Forest plots for secondary outcomes are given in Figure 3.

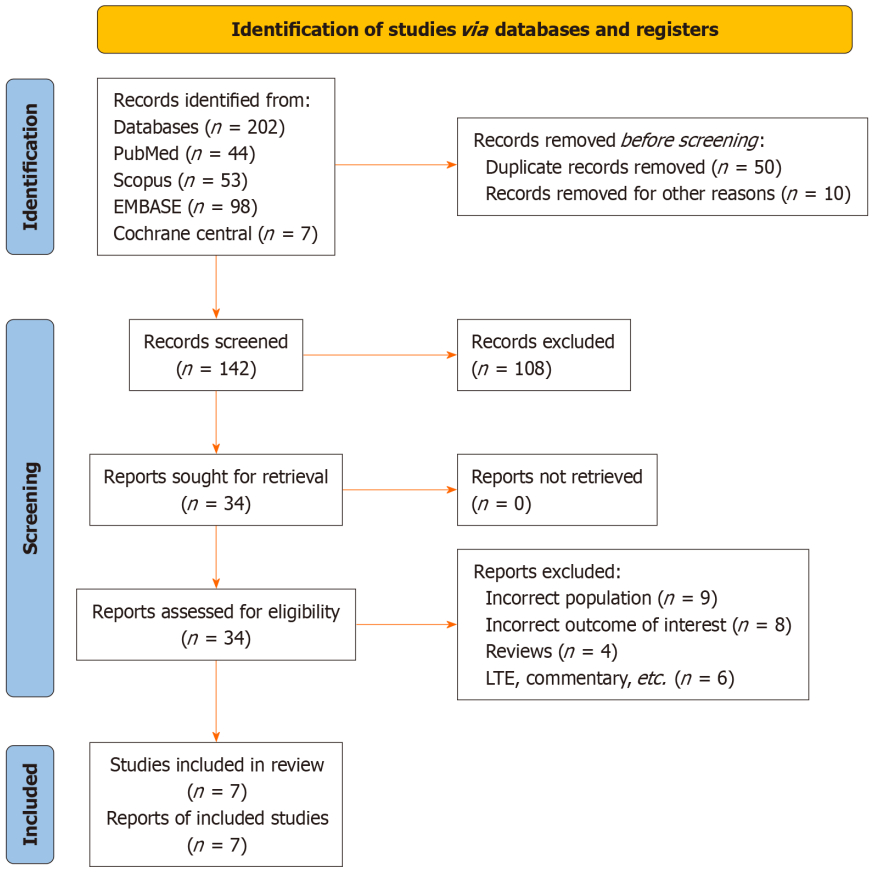

Figure 1 Preferred Reporting Items for Systematic Review and Meta-analyses flowchart. LTE: Letter to the Editor.

Sensitivity analysis

A sensitivity analysis was performed for outcomes with significant heterogeneity. In the severe hypocalcemia outcome and change in serum phosphate outcome, leave-one-out sensitivity analysis based on removing outliers resulted in a significant reduction in heterogeneity as shown in Supplementary Figure 3 (RR: 4.23; 95%CI: 0.47-38.34; I^2 = 96% to RR: 13.82; 95%CI: 5.98-31.93; I^2 = 16%) and Supplementary Figure 4 (MD: -0.47; 95%CI: -1.35 to 0.41; I^2 = 88% to MD: -0.09; 95%CI: -0.67 to 0.48; I^2 = 21%), respectively. In the case of change in serum calcium and change in serum iPTH outcomes, leave-one-out sensitivity analysis was able to show only a slight reduction in heterogeneity evident in Supplementary Figure 5 (MD: -0.33; 95%CI: -0.95 to 0.29; I^2 = 94% to MD: 0.00; 95%CI: -0.27 to 0.28; I^2 = 59%) and Supplementary Figure 6 (MD: -433.20; 95%CI: -775.12 to -91.28; I^2 = 98% to MD: -635.30; 95%CI: -765.98 to -504.62; I^2 = 85%), respectively.

Meta-regression

We assessed age, sex, serum calcium, serum phosphate, and iPTH as possible covariates for having an impact on the effect sizes for severe hypocalcemia. We found severe hypocalcemia to be significantly associated with serum phosphate (Coeff: -0.3634, P = 0.0000) only (Supplementary Table 5 and Supplementary Figures 7-12).

We also assessed age, sex, serum calcium, serum phosphate, iPTH, and alkaline phosphatase as possible covariates for having an impact on the effect sizes for mild hypocalcemia. We found mild hypocalcemia to be significantly associated with sex (Coeff: 0.0336, P = 0.0421), age (Coeff: -0.1003, P = 0.0290), and serum phosphate (Coeff: -0.1784, P = 0.0124) (Supplementary Table 6 and Supplementary Figures 13-19).

DISCUSSION

Osteoporosis is one of the common age-related challenges, being of considerable importance in postmenopausal females and other older adults. Denosumab is clinically implicated in reducing the fracture risk and increasing bone mineral density among patients with ESRD. However, the adverse effects of the drug are not clearly demonstrated. Therefore, we conducted this systematic review and meta-analysis, which showed a statistically significant association of denosumab use with mild hypocalcemia, very severe hypocalcemia, and decreased serum iPTH. However, there were no significant differences between the control group and ESRD group participants for severe hypocalcemia and changes in serum calcium and phosphate levels following denosumab administration. The meta-regression findings indicated that age, sex, and serum phosphate were potential covariates that significantly influenced the incidence of mild hypocalcemia in patients with ESRD on denosumab treatment. Serum phosphate was also found to be a significant covariate for the

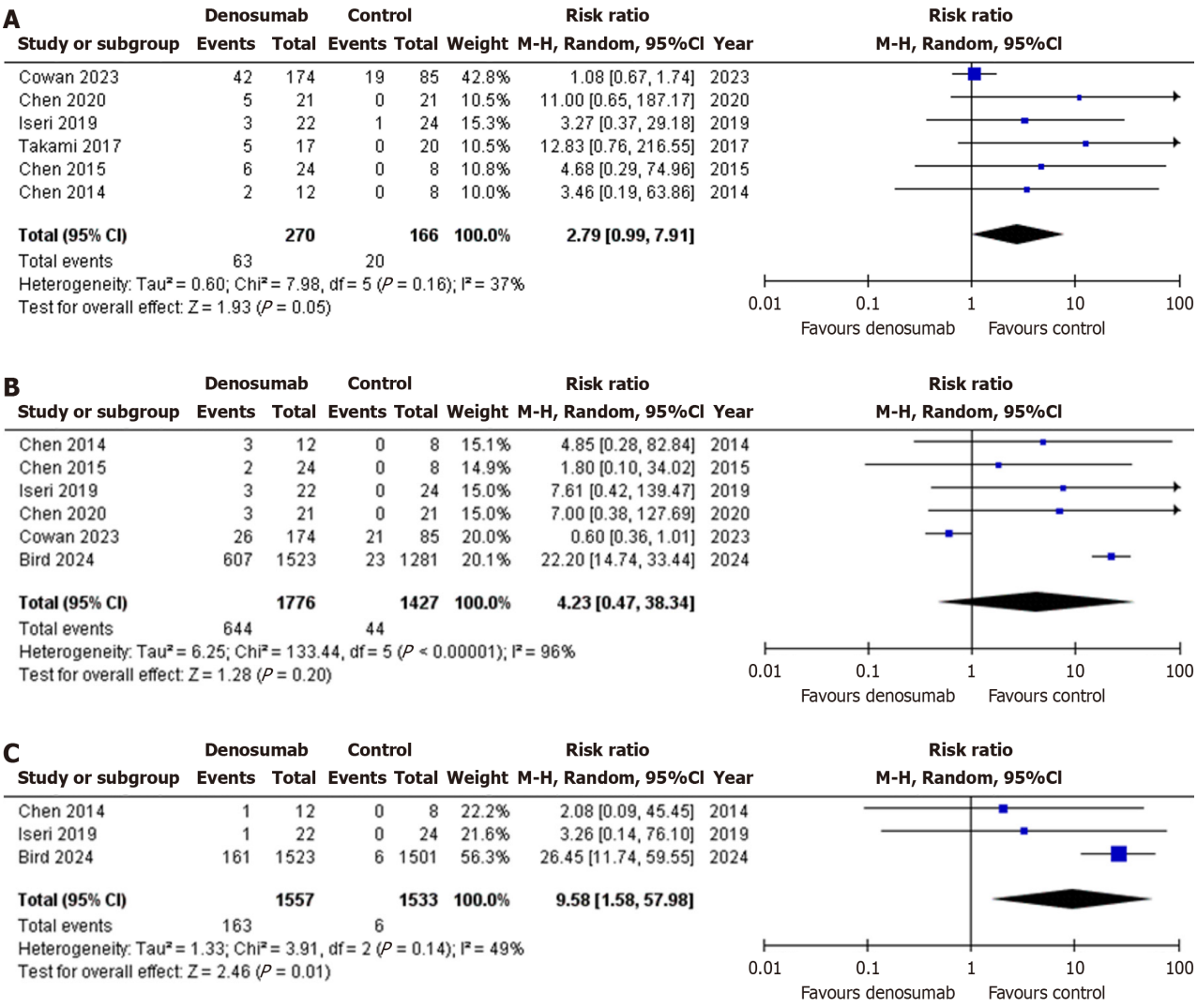

Figure 2 Forest plots for primary outcomes. A: Mild hypocalcemia; B: Severe hypocalcemia; C: Very severe hypocalcemia. CI: Confidence interval.

incidence of severe hypocalcemia.

Denosumab, a human monoclonal antibody, exerts its action by suppressing the maturation and function of osteoclasts, decreasing bone resorption. The inhibition of receptor activator of nuclear factor kappa-B-ligand and subsequent reduction in bone resorption leads to clinically effective improvement in bone mineral density and skeletal-related events[24]. Denosumab-induced hypocalcemia can be explained by a decline in calcium levels in the blood secondary to a reduction in bone resorption. Moreover, denosumab causes impairment in the renal production of calcitriol, resulting in the development of hypocalcemia[21,25,26]. While preventing osteoclast-mediated bone resorption, denosumab disrupts the PTH-driven maintenance of calcium levels in the blood, resulting in hypocalcemia. The simultaneous increase in PTH at non-skeletal sites lowers the serum phosphate levels[27]. Notably, among patients with late-stage CKD, the bones become the primary source of serum calcium levels. This is further supported by the notion that patients with late-stage CKD on dialysis and a regular diet with calcium supplements exhibit calcium efflux from the skeletal system[28].

In our focused population comprising patients with advanced CKD, iPTH can be utilized as a useful bone turnover biomarker at the population level. Extremely high concentrations of iPTH are indicative of high-turnover bone pathology, very low levels of iPTH represent low-turnover bone disease[29]. In this study, denosumab administration was significantly associated with a decrease in iPTH levels. A retrospective analysis conducted by Tsvetov *et al*[30] concluded that pretreatment creatinine and albumin-adjusted serum calcium levels were the strongest predictors of denosumab-induced hypocalcemia in postmenopausal females with osteoporosis. The rise in the rates of hypocalcemia was found to be parallel to the decline in eGFR. Therefore, serum calcium monitoring for early identification of severe hypocalcemia is recommended in high-risk individuals. The retrospective multivariate analyses suggest CKD and baseline hypocalcemia as risk factors for the development of denosumab-induced hypocalcemia[31]. However, Saito *et al*[32] reported that renal dysfunction did not play a significant role in the risk of denosumab-induced hypocalcemia.

Our study demonstrated a significant association between the incidence of denosumab-induced mild hypocalcemia and age, sex, and serum phosphate. Serum phosphate was also found to be a significant covariate in the development of severe hypocalcemia in patients with ESRD treated with denosumab. Several studies have investigated the role and

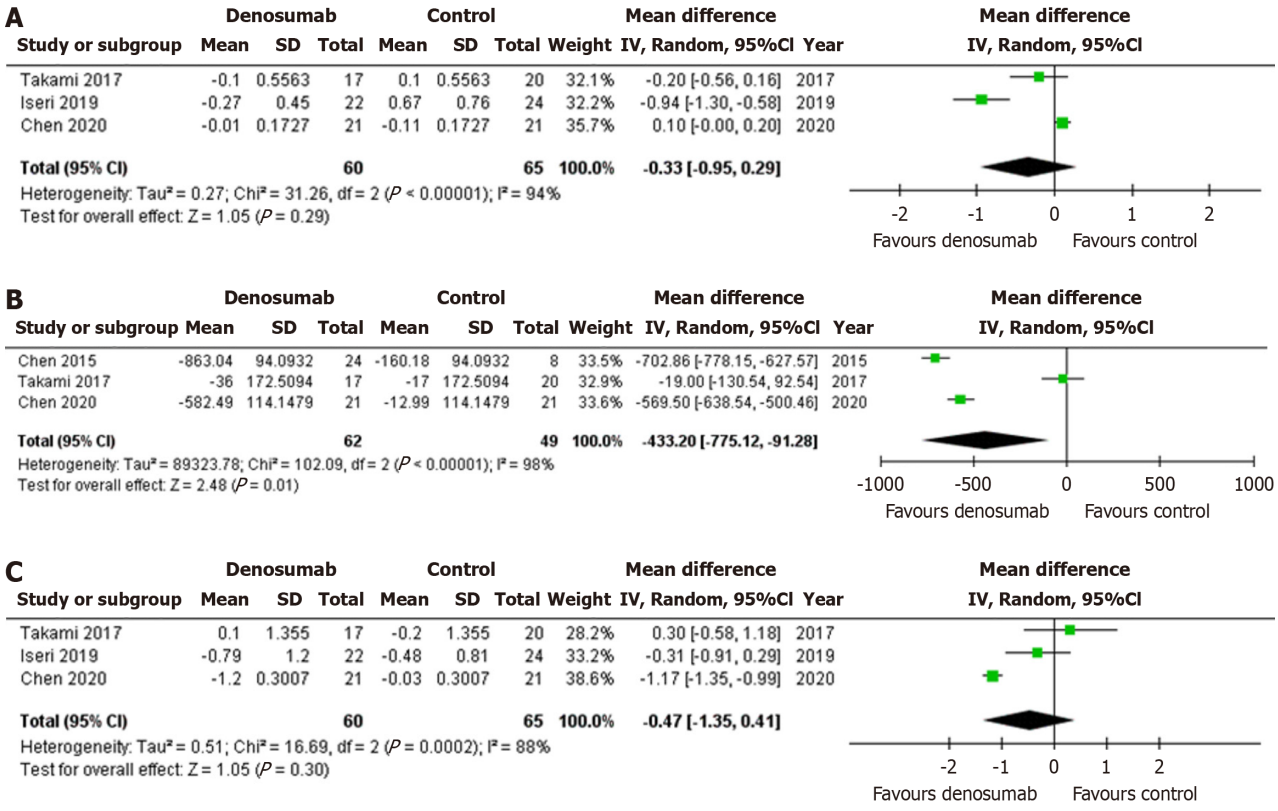

Figure 3 Forest plots for secondary outcomes. A: Change in serum calcium; B: Change in serum intact parathyroid hormone; C: Change in serum phosphate. CI: Confidence interval.

statistical significance of different risk factors in the development of denosumab-induced hypocalcemia. Sex does not play a predictive role in the incidence of denosumab-induced hypocalcemia[30,33]. However, denosumab-treated males are found to be significantly older compared to denosumab-treated females, with the former having more advanced disease and lower eGFR[33]. Conversely, Spångeus *et al*[34] identified males, severe renal failure, and pretreatment denosumab as important predictive factors. While diabetes is not explicitly investigated in existing studies for its correlation with the risk of denosumab-induced hypocalcemia in patients with ESRD, higher rates of baseline diabetes are observed in patients with lower eGFR[18].

While we observed a statistically significant association between serum phosphate levels as a potential covariate in mild and severe hypocalcemia, the sensitivity analysis revealed significant heterogeneity for changes in serum phosphate levels and severe hypocalcemia. A leave-one-out sensitivity analysis demonstrated a significant reduction in heterogeneity. However, only a slight reduction was observed when leave-one-out sensitivity analysis was performed for changes in serum calcium levels and iPTH. Despite recruiting a very large cohort of patients, Cowan *et al*[18] failed to undertake group matching, resulting in statistically significant differences in the baseline variables of the denosumab and control group participants. Serum phosphate heterogeneity in the associations of denosumab use and severe hypocalcemia prompted the removal of the study from the meta-analysis in order to yield more valid findings[35]. Dietary factors, age, genetics, sex, and season all tend to have a significant influence on serum phosphate levels[36]. Phosphate control is inherently impaired in patients with ESRD without any remaining renal function, stimulating hyperphosphatemia. However, other patient-related factors should be taken into account[37]. The existence of age and sex differences in the levels of serum and phosphate levels also provides a valid reason for the studies to utilize matched control and intervention group data in order to yield reliable findings[38].

In this study, we conducted a comprehensive systematic review and meta-analysis of incidence and predictors of hypocalcemia in patients with ESRD on denosumab therapy. While our study was able to identify clinically relevant findings and delineate age, sex, and serum phosphate as predictors of mild hypocalcemia associated with denosumab use in patients with ESRD, there are a few limitations. The high inter-study heterogeneity observed in the analysis can be attributed to methodological variation across the studies, predominantly the differences in the study design. The retrospective cohort by Cowan *et al*[18], which was identified as the source of heterogeneity as per the sensitivity analysis, did not account for the significant baseline differences between the denosumab and bisphosphonate groups. Due to the small numbers of patients with low eGFR and significant baseline differences between those prescribed denosumab and bisphosphonates, the study did not employ matching or weighing techniques to balance the groups. Due to incomplete population coverage, as the study excluded approximately 39% of the Ontario population due to their residence outside of the hospital, it led to a loss of 142000 patients, possibly introducing bias. Moreover, a significant proportion of new denosumab users (approximately two-thirds) did not have calcium levels monitored post-initiation. This lack of comprehensive monitoring may have resulted in underreporting of hypocalcemia cases, especially in those who develop

symptoms. The study also could not account for over-the-counter calcium and vitamin D3 use, which may impact the risk of hypocalcemia. Moreover, the lack of control groups and the potential for selection bias in the included case series may also account for the high inter-study heterogeneity[20]. The cohort study by Takami *et al*[20] was also identified as a source of heterogeneity in our paper and had the following limitations: It had a small sample size and lacked a randomized controlled group, which limits its ability to generalize findings and assess the safety and efficacy of denosumab comprehensively. The lack of bone mineral density measurements at multiple sites (*e.g.*, lumbar spine, total hip, femoral neck) in the referenced study meant that our analysis was limited to the distal third of the radius. This site-specific focus may have contributed to variability in understanding the broader effects of denosumab on bone health.

Our study findings may contribute to the improvement of the management of patients with ESRD undergoing denosumab therapy. The identification of the incidence and the predictive factors of hypocalcemia defines several future implications across the different key areas. One of these is the development of risk stratification tools, which facilitate the recognition of high-risk patients with ESRD who have a greater likelihood of developing hypocalcemia. Statistically significant predictors such as age, baseline osteoporosis, and baseline diabetes mellitus can inform strategies to optimize denosumab therapy for patients with ESRD and prevent the development of hypocalcemia post-denosumab treatment. The study findings may also instigate the development of clinical trial protocols, which are more focused on denosumab treatment in patients with ESRD. In addition to these prospects, the research findings are suggestive of patient monitoring and improving patient care by minimizing the number and severity of adverse effects.

CONCLUSION

Denosumab, used as a treatment for ESRD, can lead to either mild, moderate, or severe hypocalcemia post-administration. The results show a non-significant decrease in serum calcium and phosphate levels but a statistically significant decrease in serum PTH levels with denosumab administration. Therefore, it is important to provide integrated care, calcium and vitamin D supplementation, and CKD-mineral bone disorder optimization. Serum calcium monitoring is recommended for early detection of severe hypocalcemia in high-risk patients.

FOOTNOTES

Author contributions: Moeed A, Siddiqui AH, Fahim MAA, Salman A, and Surani SR participated in the conceptualization, data curation, investigation, methodology, project administration, resources, supervision, validation, visualization, and writing of the original draft; Shaikh M, Batool F, Mari T, Musani S, Fareed M, Rehan R, Hassni A, Nizami U, and Amir A were involved in project administration and writing of the original draft; Fahim MAA, Moeed A, Siddiqui AH, and Surani SR were involved in the formal analysis, project administration, supervision, validation, visualization, and writing, reviewing, and editing; All authors read and approved the final manuscript.

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