VENOUS CONGESTION IN SEPTIC SHOCK: A SYSTEMATIC REVIEW AND PILOT STUDY

BY: ROSS PRAGER, MD

A thesis submitted to the School of Graduate Studies in partial fulfillment of the requirements for the degree of Master of Science in Health Research Methodology,

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ABSTRACT

This thesis consists of two related studies presented as separate manuscripts. This research focuses on understanding venous congestion in critically ill patients.

First, we conducted a systematic review to summarize evidence regarding venous congestion in critically ill patients, particularly those with septic shock, to understand its association with organ dysfunction and outcomes. We included observational studies that used the Venous Excess Ultrasound (VeXUS) score in critically ill patients.

Following the systematic review, we performed a retrospective analysis of a previously conducted pilot study to assess the velocity time integral (VTI)-VeXUS ratio, a novel hemodynamic marker that we propose, to better understand integrated hemodynamic measurements that consider both arterial and venous physiology.

Despite advances in sepsis management, venous congestion remains an under-recognized component of shock. This thesis contributes to the growing body of evidence advocating for a more nuanced approach to resuscitating patients with septic shock.

ACKNOWLEDGEMENTS

I would like to sincerely thank my thesis supervisors. **Dr. Bram Rochwerg** provided invaluable mentorship and guidance throughout this process. **Dr. Kim Lewis** was instrumental in refining the methodological aspects of the studies, and **Dr. Sarah Neil-Sztramko** offered critical insight into knowledge translation and study design.

I would also like to acknowledge the many colleagues, mentors, and research staff who contributed to this work, either through direct collaboration or ongoing support. I extend a

special thank you to Dr. John Basmaji for his mentorship on both studies and during my early research career.

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DECLARATION OF ACADEMIC ACHIEVEMENT

This thesis is submitted in partial fulfillment of the requirements for the Master of Science program in Health Research Methodology at McMaster University. The work is presented as a sandwich thesis, consisting of two separate but related manuscripts.

I participated in all aspects of the research, including study conception and design, data collection, analysis, manuscript writing, and presentation. A Physician Services Inc. (PSI) Foundation Resident Grant supported the original research on which the pilot study is based; no other funding was received for this research.

I supervised the systematic review and meta-analysis, including protocol development, data abstraction, risk of bias assessment, and statistical analysis, in collaboration with my supervisors and co-investigators. The pilot study was designed with input from my supervisory committee, and I was responsible for developing the research protocol, obtaining ethical approvals, designing the study, conducting the analysis, and preparing the manuscript.

INTRODUCTION

The Burden of Septic Shock

Septic shock remains a leading cause of mortality among critically ill patients, accounting for over 60% of shock-related admissions to intensive care units (ICUs) worldwide.[1,2] Mortality from septic shock is high, often approaching 40%, and healthcare expenditures related to septic shock exceed one billion Canadian dollars annually in Ontario alone.[3,4] Acute kidney injury (AKI) is a significant contributor to the morbidity associated with septic shock, occurring in approximately 50% of patients and leading to worse clinical outcomes.[5] Patients who develop AKI in the context of septic shock experience increased mortality, prolonged ICU stays, and greater dependence on organ support therapies such as renal replacement therapy (RRT).[5,6] Understanding and addressing the contributors to AKI in septic shock may help improve outcomes.

The Myth of the "Classic" Phenotype of Septic Shock

Historically, clinicians have categorized septic shock primarily as distributive "warm" shock, characterized by high cardiac output, vasodilation, and preserved ventricular function. Recent evidence, however, suggests that this classic paradigm is incomplete, as alternative and mixed profiles with low stroke volume and cardiac dysfunction are increasingly recognized.[7-11] Despite this evolving understanding, venous congestion remains poorly integrated into the pathophysiological framework of septic shock.[12] The predominant educational and clinical focus on arterial hemodynamics and forward flow may neglect venous congestion as an important contributor to organ injury in sepsis.

Venous Congestion as an Important Hemodynamic Paradigm

Venous congestion occurs when elevated venous pressures cause organ hypoperfusion by reducing the arterial-to-venous pressure gradient essential for tissue-level perfusion.[13-21] Although the importance of elevated central venous pressure (CVP) has been described for decades, only recently has it garnered widespread interest from the critical care community.[19] High venous pressures can be transmitted retrograde, impairing venous drainage, causing edema, and subsequently leading to organ dysfunction, particularly in encapsulated organs such as the kidneys and liver.[19] There are also local contributors to AKI, with intrabdominal and pulmonary processes influencing blood flow in abdominal organs. [19] Although historically linked to adverse outcomes like AKI, elevated CVP alone lacks accuracy in predicting AKI,[19] highlighting the need for novel approaches to identify and quantify venous congestion at the bedside.

Biological Mechanisms of Organ Injury in Venous Congestion

Emerging evidence suggests that venous congestion may trigger organ dysfunction through mechanisms such as elevated venous pressures, tissue edema, inflammation, and impaired microcirculatory function.[22] A translational biology study by our group demonstrated higher soluble endothelial markers in congested patients (unpublished). At the microcirculatory level, elevated venous pressures reduce arterial-to-venous gradients, compromise oxygen delivery, and create a "compartment syndrome"-like scenario in organs such as the kidneys.[23,24] These physiological disturbances may initiate cascades of inflammatory and ischemic injury, contributing to septic shock-related organ failure.

Measurement of Venous Congestion

Traditionally, clinicians have relied on CVP as an indirect marker of congestion; however, its predictive value for organ dysfunction is limited.[19] For example, a CVP above 12mmHg has a

sensitivity of 83% and specificity of 33% for predicting AKI.[19] Several factors may explain this limitation. First, right atrial pressure may not represent the pressure experienced at the kidney due to thoracic and abdominal pressures. Next, the compliance of the venous system may influence the extent to which retrograde flow is transmitted to the end organs. Finally, it is possible that pressure is not the primary factor affecting congestive abnormalities at the organ level, and that flow abnormalities (as seen on Doppler) are more relevant.

Recently, Doppler ultrasound has emerged as a more precise, non-invasive method to assess venous congestion at the organ level.[19] Doppler ultrasound evaluates venous flow abnormalities in the hepatic, portal, and renal veins, and has been standardized through the Venous Excess Ultrasound Score (VeXUS).[19] Compared with CVP, which has a sensitivity of 83% and specificity of 33% for predicting AKI after cardiac surgery, a VeXUS score of 3 is 96% sensitive and 27% specific.[19] Although thresholds of congestion that best predict organ injuries for various populations remains an ongoing research question, this advancement provides a direct assessment of congestion at the bedside, potentially facilitating early and targeted interventions.

The VeXUS Score

The VeXUS score has shown promise as a reliable marker for identifying clinically relevant venous congestion.[12,19] It integrates Doppler ultrasound findings from the hepatic vein (HV), portal vein (PV), and intrarenal veins (IRV) into a simple grading system, correlating with outcomes such as AKI, RRT, and mortality in critically ill populations.[12-15,18,19,25]

To calculate the VeXUS score, a clinician first performs an inferior vena cava (IVC) assessment. If the IVC is not dilated (<2 cm), the score is zero (not congested). If the IVC is dilated (>2 cm), the clinician then performs HV, PV, and IRV Doppler assessments. If there are no severe

abnormalities in these veins, the score is 1. If there is only one severe abnormality, the score is 2 and considered congested. If there are two or more severe abnormalities, the score is 3 (severely congested). The Doppler signal abnormalities are shown in Figure 1. Of note, for the IRV, the venous signals are below the baseline.

Figure 1

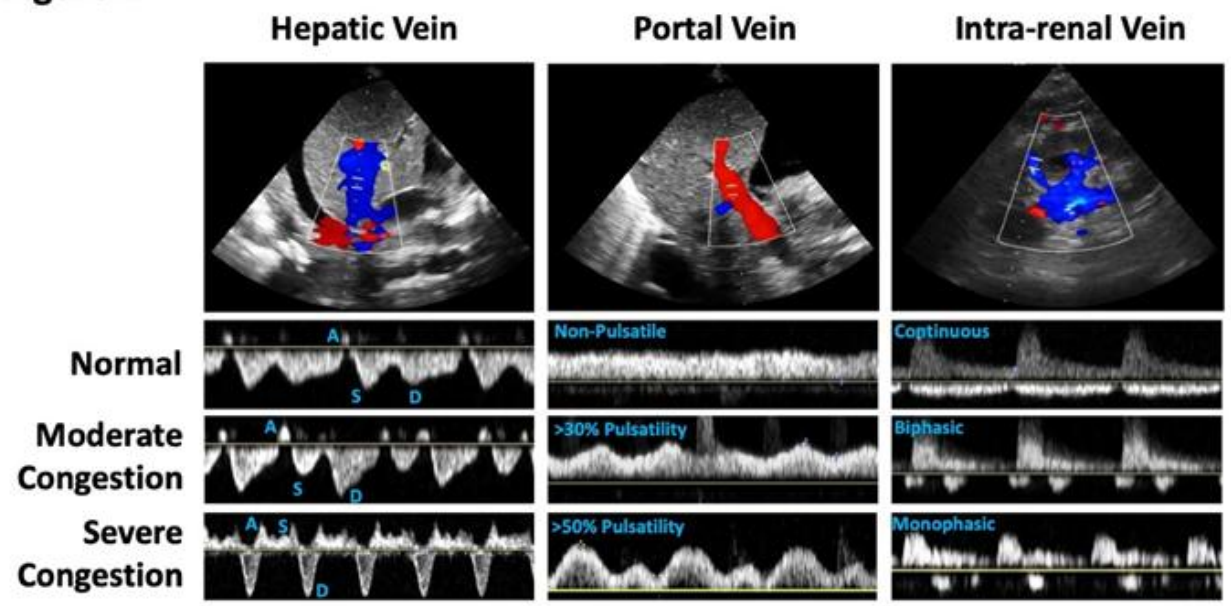

Figure: 1Doppler abnormalities in the portal vein, hepatic vein, and intrarenal vein. Redisplayed here with permission under Open License from Prager et al. 2023.

Recent studies by our group have further validated the utility of the VeXUS score in patients with septic shock, demonstrating an association between congestion and an increased hazard for requiring RRT (unadjusted HR 3.35, 95% CI 0.94–11.88, p=0.06).[12] Despite these promising findings, additional evidence is required to fully understand the diagnostic role of VeXUS in septic shock and its potential therapeutic interventions.

Venous Congestion in Sepsis

Venous congestion may occur early in septic shock due to right ventricular dysfunction, excessive fluid resuscitation, or a combination of both.[12,14] While early fluid administration is crucial for septic shock resuscitation, the balance between adequate resuscitation and fluid overload is delicate and poorly understood.[26] There is emerging recognition that venous congestion, alongside cardiac dysfunction, may play a role in the pathogenesis of organ failure in patients with sepsis.[14,24,27-30] This is analogous to the left-sided circulation, where the interplay between volume status and left ventricular function generates pulmonary edema (left-sided congestion). Further research is necessary to delineate the prevalence, timing, and clinical impact of venous congestion specifically within the septic shock population, given its distinct pathophysiology.

Integrating Venous-Arterial Physiology in Sepsis

Historically, resuscitation strategies in sepsis have emphasized arterial physiology and forward flow, largely neglecting venous pressures.[31-33] Recent evidence suggests that an isolated evaluation of either venous or arterial systems provides an incomplete picture of patient hemodynamics.[34,35] Integrative metrics, such as the Pulmonary Artery Pulsatility Index (PAPi), have demonstrated the value of a combined arterial-venous assessment in heart failure patients.[36-38] Extending this principle, our team proposed the VTI-VeXUS ratio, a novel metric that integrates stroke volume (forward flow) and venous congestion (back flow), offering a more comprehensive assessment of circulatory function. This measure addresses limitations inherent in conventional hemodynamic assessments focused on forward flow or congestion alone.

Final Knowledge Gaps

Despite significant progress, critical knowledge gaps remain regarding the implications of venous congestion in patients with septic shock. Notably, the prevalence and clinical thresholds of venous congestion associated with harm in septic shock remain undefined.[16] While the VeXUS score has demonstrated predictive capability for organ injury, its integration with arterial flow indices, such as the VTI-VeXUS ratio, has not yet been thoroughly validated. This thesis aims to address these gaps by quantifying the relationship between venous congestion and organ dysfunction across multiple studies using a systematic review with meta-analysis and by exploring the clinical utility of the novel VTI-VeXUS index to guide fluid resuscitation strategies.

MANUSCRIPT 1 – Systematic Review

TITLE Venous Congestion Excess Ultrasound (VeXUS) and adverse outcomes for critically ill adults: a systematic review with meta-analysis

RUNNING TITLE: VeXUS systematic review

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Ethics Approval: Not required for systematic reviews.

BACKGROUND

Acute kidney injury (AKI) is associated with morbidity and mortality in critically ill patients. [1,2] Venous congestion is increasingly recognized as an important cause of AKI in acutely ill patients. [3-8] Preliminary studies have identified an association between venous congestion and AKI, the need for renal replacement therapy (RRT), and death, although the underlying pathophysiology has not been fully delineated. [3-10]

Venous congestion can be identified using invasive and non-invasive approaches. Central venous pressure (CVP) was traditionally used to assess venous congestion, and although studies have demonstrated an association between high CVP and AKI[11], this association lacks accuracy, likely due to the complex interplay between venous pressure, venous flow, and cardiac function. [3,12] Doppler ultrasound has emerged as a non-invasive tool to quantify venous congestion through assessment of the portal vein (PV), hepatic vein (HV), and intrarenal vein (IRV). [3-5,7-9,13] These measures have been combined into the Venous Excess Ultrasound Score (VeXUS), with scores of 0 or 1 representing 'not congested' and scores of 2 or 3 representing 'congested. [3,14,15]' In addition to the safety, portability, and repeatability of Doppler

ultrasound[16], VeXUS is measured at the organ level, which may increase the specificity for predicting organ injury.

While multiple studies have examined the association between venous congestion and AKI in critically ill patients, the certainty of evidence is limited by small sample sizes, heterogeneous populations, different thresholds for determining venous congestion, and observational designs. The primary objective of this systematic review is to summarize the association between VeXUS and AKI in critically ill patients. Secondary objectives include assessing the association between venous congestion and other patient-important outcomes such as hospital length of stay, ICU length of stay, use of renal replacement therapy, and death.

METHODS

Reporting and Registration

We designed this review in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines. [17] We registered the protocol on Open Science Framework (OSF) prior to data collection (Link: https://osf.io/w5be7/), and there were no protocol deviations. This review focuses only on the VeXUS score, with a plan to report the findings of the organ-specific venous congestion assessments in separate manuscripts.

Patient Participation

The study protocol was reviewed by our patient partner (VY), who has experienced critical illness. This individual helped to prioritize outcomes for this systematic review, reviewed the results, and contributed to the interpretation of the findings.

Data sources and searches

We designed the search with help from a research librarian (CS). The search strategy is available in Appendix 1. We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and CINAHL Plus from inception until October 10, 2024, without language restriction. We also searched for unpublished studies and conference abstracts from the Society of Critical Care Medicine, European Society for Intensive Care Medicine, and International Society of Intensive Care Medicine from 2021 to October 10, 2024. If potentially eligible abstracts were identified, we contacted the authors for full data. All references and citations of potentially eligible studies were screened, as well as reference lists from relevant systematic reviews identified in our search.

Study Selection

Eligibility Criteria

We included studies if the study sample included: 1) adults (age ≥16, mixed populations if >75% were adults, or if the study reported outcomes from adults separately from children), 2) patients admitted to an ICU (including cardiac surgery, coronary care unit, surgical and medical patients), or undergoing cardiac surgery, and 3) patients who had a VeXUS score performed. Eligible studies needed to report data that describe an association between venous congestion and any outcomes of interest (see below).

We included observational studies that reported and compared a congested to a non-congested cohort (definitions below). We excluded animal studies, case studies, reviews, and observational studies that did not have a comparator cohort.

Screening

We used Covidence software (Melbourne, Australia) for screening in two stages. First, two authors (RP and SP) screened all titles and abstracts independently and in duplicate. Any citation deemed potentially relevant by either reviewer was advanced to full-text review. We reviewed all full texts independently and

in duplicate, with discrepancies resolved through consensus. We recorded reasons for exclusion at the full-text review stage.

Data extraction and risk of bias assessment

Study Demographics

We independently extracted data in duplicate using pre-piloted case report forms, resolving discrepancies through consensus. We recorded the author name, country of the corresponding author, year of publication, study design, study type, setting (general ICU, cardiac surgical ICU, coronary care unit), timing of venous congestion evaluation, threshold for congestion (e.g., VeXUS ≥2 as a dichotomous scale), eligibility criteria, sample size, event rate for the venous congestion and non-venous congestion arms, and measure of association.

Risk of Bias Assessment

We independently performed a risk of bias assessment in duplicate using the QUality In Prognostic Studies (QUIPS) tool, resolving discrepancies through consensus discussion. [18] Signalling questions are available in Appendix 2.

Outcomes

We focused on the following outcomes of interest:

1. Acute kidney injury (as defined by individual study authors using validated scoring system)
2. Severe acute kidney injury (as defined by individual study authors using a validated scoring system, e.g., Stage 2 or 3)
3. Hospital length of stay (LOS)
4. ICU LOS
5. Use of renal replacement therapy (RRT)

6. Mortality at the longest point of follow-up
7. Functional status post-discharge (as defined by individual study authors using a validated assessment)
8. Cognitive outcomes post-hospital discharge (as defined by individual study authors using a validated assessment)

Data Synthesis

We used RevMan (version 5.4.1) for statistical analysis. We pooled measures of association using inverse variance weighting and a random effects model. When possible, we converted measures of association to odds ratios for analysis. We pooled only the unadjusted measures of association, as few of the included studies reported adjusted measures. We report pooled odds ratios for dichotomous outcomes (AKI, RRT, and mortality) and mean differences for continuous outcomes (hospital LOS, ICU LOS), along with 95% confidence intervals. We assessed statistical heterogeneity by visual inspection of the forest plots, the I^2 statistic, and the Chi-squared test.

Different thresholds of test positivity

Various thresholds of test positivity for VeXUS can be used; therefore, we captured the thresholds used in each individual study to define venous congestion. If not specified, we classified VeXUS 2 and 3 as congested, and VeXUS 0 and 1 as not congested.

Publication and reporting bias

We assessed potential publication bias using a funnel plot. We planned to perform the Egger test if more than 10 studies reported an outcome of interest.

Subgroup Analyses

We planned to conduct subgroup analyses; however, due to imprecision and the limited number of studies, we did not perform these analyses. Planned subgroup analyses included comparisons between

cardiac surgical and non-cardiac surgical patients, as well as between studies with low and high risk of bias.

Dealing with missing data

If we encountered missing data, we attempted to contact study authors for additional information. We considered the degree of missingness in our risk of bias assessments.

Assessing the certainty of evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of evidence for each outcome.[39] The GRADE system classifies the aggregate body of evidence as very low, low, moderate, or high. We included a summary of findings table and evidence profile in the results, showing the GRADE assessments and pooled analysis for each outcome. We also used GRADE narrative language to describe associations. We used the null as the threshold for imprecision ratings, except for length of stay, for which we considered a 1-day difference to be clinically important. [19]

Results

Of 6,840 citations, we screened 128 full-text articles and included 9 studies in the final analysis. Figure 1 (PRISMA flow diagram) provides a detailed breakdown of the screening process. We identified four additional unpublished studies as potentially relevant. Two authors did not respond after three separate attempts to obtain data, one provided detailed outcome-level data and was included, and the fourth indicated that results were still unpublished and unavailable for inclusion in this review.

Study Characteristics and Demographics

All nine included studies were prospective observational studies. These studies included general medical ICU populations (n=4), cardiac surgical patients (n=3), and cardiac ICUs (n=2) with variable admission

etiologies. Sample sizes ranged from 19 to 145 patients, with a total pooled population of 769 participants.

In all studies, the VEXUS score was used to define venous congestion. Thresholds varied slightly across studies (Figure 2). Table 1 summarizes key study characteristics, including the time points for Doppler assessment, sample size, ICU type, and outcomes reported. An insufficient number of studies reported severe AKI, functional status, or cognitive outcomes post-hospital discharge to be included.

Acute Kidney Injury (AKI)

Six studies examined the association of VEXUS with AKI (n=732 total patients). Of these, 75 out of 159 patients in the congested group had AKI, and 170 out of 573 patients in the non-congested group had AKI. Pooled analysis demonstrated that venous congestion may be associated with AKI (OR 2.34, 95% CI: 0.99 to 5.49, low certainty evidence) (Figure 3). The certainty of evidence was rated as low due to the high risk of bias in QUIPS domains for study participation and confounders. However, the GRADE score was increased from very low based on the magnitude of association (Figure 9 and Appendix 3).

Renal Replacement Therapy

Seven studies examined the use of RRT (n=593 patients). Of these, 186 were in the congested group, with 51 requiring RRT (27.4%), compared to 93 of 407 patients (22.9%) in the non-congested group requiring RRT. There was an uncertain association between venous congestion and the use of RRT (OR 1.17, 95% CI: 0.71 to 1.94, very low certainty; Figure 4 and Appendix 3).

Mortality

Mortality data were available from 7 studies (n=706 patients). In the congested group, 45 of 193 patients died (23.3%), compared to 109 of 513 patients (21.2%) in the uncongested group. There was an uncertain

association between venous congestion and mortality (OR 1.15, 95% CI: 0.72 to 1.84, very low certainty; Figure 5 and Appendix 3 and 4).

Length of Stay (LOS)

Four studies reported on ICU LOS (n=370 patients). There was an uncertain association between venous congestion and ICU LOS (MD 0.45 days longer in the congested group, 95% CI: 0.07 days shorter to 0.97 days longer, very low certainty; Figure 6 and Appendix 3 and 4). Hospital LOS was reported in four studies (n=372 patients). There was an uncertain association between hospital LOS and venous congestion (MD 1.32 days longer in the congested group, 95% CI: 1.52 days shorter to 4.16 days longer, very low certainty; Figure 7 and Appendix 3 and 4).

Publication Bias

There was no evidence of publication bias for any outcomes of interest, partly due to the low number of included studies (Figure 8 and Appendix 4).

Discussion

Our systematic review and meta-analysis demonstrate that venous congestion, as identified by the VExUS score, may be associated with an increased risk of AKI in critically ill patients, with a pooled OR of 2.34 [95% CI: 0.99 to 5.49]. No significant associations were identified for the secondary outcomes of RRT, mortality, ICU LOS, or hospital LOS. The certainty of evidence was graded as *low* for AKI and *very low* for other outcomes due to small sample sizes, variable associations, and high risk of bias, driven primarily by the QUIPS domains of study participants and confounders.

In contrast to previous studies that demonstrated an association between congestion and other outcomes such as RRT or death[15,20], when pooled, the association with AKI is the most notable. This may be partly related to the high susceptibility of the kidney to congestive injury due to its encapsulation. Unlike other

organs that can swell when congested, the kidney is surrounded by fascia, so when it swells, compliance rapidly decreases. This results in local compartment syndrome physiology that leads to tissue-level impairments in both arterial and venous renal flows.

Although venous congestion has been associated with an increased *hazard ratio* for RRT or death in multiple studies, no statistically significant association was found when calculating the pooled *odds ratios* in this study. [15,20] As observed in our local pilot study assessing venous congestion in septic shock[15], survival curves for RRT or death diverge quickly in the first few days; however, they converge by day 30. Because hazard ratios incorporate time to event, whereas odds ratios do not, this separation is captured in differences in hazard ratios. In this meta-analysis, odds ratios were pooled due to heterogeneity in reporting methods of association. If patients receive therapies such as diuretics or inotropes *due to their congestion*, this may have attenuated the association between congestion, RRT, and death at later time points. Across all studies, co-interventions were poorly reported, resulting in a rating of high risk of bias in this QUIPS domain.

Although AKI is often used as an endpoint, its importance to patients when dialysis or death do not occur is questionable. We advocate for more patient-centered outcomes such as RRT, death, or composites like MAKE-30 (major adverse kidney events within 30 days, including death, RRT, or persistent AKI) instead of AKI in isolation. Other outcomes that capture the multi-organ impact of venous congestion, such as organ support-free days, would also be appropriate as they are important to both patients and the health system.

Our work raises an important question: is venous congestion simply a prognostic marker of illness severity, or is it a modifiable therapeutic target? Venous congestion is highly correlated with ventricular dysfunction. Do patients with worse ventricular function simply have worse outcomes, regardless of their congestion status? If we target venous congestion as a therapeutic target, will organ failure improve? These questions need to be addressed through prospective interventional research controlling for

ventricular function as a potential confounder. Additionally, trials are needed to understand whether and how acting on venous congestion may reduce congestive organ injury.

Limitations

Findings from our systematic review should be interpreted with caution due to the limitations of the included studies, such as small sample sizes, observational designs, and high heterogeneity in both study design and reporting. The risk of bias of included studies was high in key domains, including participant selection and confounding. While we attempted to mitigate missing data, this was limited by incomplete author responses. The small number of studies also precluded meaningful subgroup analyses. A final limitation is the questionable patient importance of isolated AKI. Our patient partner highlighted that isolated AKI without dialysis or death was of less importance to them and other ICU survivors. We have taken this into account and, for our future prospective work, have chosen more patient-important outcomes such as the need for RRT or death.

Future Directions

Future research should prioritize large, multicenter prospective cohort studies with standardized Doppler protocols and robust data on co-interventions and baseline echocardiographic variables. Studies should also explore the optimal thresholds for defining congestion and investigate whether early, targeted interventions can improve patient-important outcomes. Ongoing trials, such as Andromeda-VEXUS[14], will be crucial in addressing these gaps and clarifying the role of venous congestion in critical care. Controlled trials will eventually be needed to demonstrate that mitigating and treating congestion attenuates organ injury.

Conclusion

While the VExUS score shows promise as a marker of venous congestion, current evidence is insufficient to draw definitive conclusions about its prognostic or therapeutic significance. High-quality, prospective

studies are urgently needed to determine whether venous congestion represents a modifiable target for improving outcomes in critically ill patients.

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Table 1. Study Demographics

Author Name	Country, Year	Study Design, Setting	Timing and Threshold for Venous Congestion	Eligibility Criteria	Sample Size	Outcome (Measurement period)	Event Rate Congested	Event Rate Not Congested	Measure of Association (95% CI)
Andrei	France 2023	Prospective Cohort General ICU	Day 1 VExUS ≥ 2	Adults (≥ 18y), admitted to ICU, without chronic atrial fibrillation, or mechanical cardiac assistance	145	AKI (7 Days)	8/23	60/122	OR 0.55 (0.22 to 1.39)
						Mortality (28 Days)	5/23	34/122	OR 0.68 (0.24 to 1.97)
Beaubien-Souligny	Canada 2020	Prospective Cohort Cardiac Surgery ICU	Day 1 VExUS ≥ 2	Non-critically ill patients ≥18 years old undergoing cardiac surgery with the use of cardiopulmonary bypass	145	AKI (28 Days)	19/32	30/113	OR 4.04 (1.78 to 9.18)
						RRT (28 days)	0/32	0/113	Not estimable
						Mortality (hospital)	1/32	0/113	OR 10.81 (0.43 to 271.86)
						ICU LOS (days)	2.07 (SD 2.61)	1.79 (SD 2.17)	MD 0.28 (-0.71 to 1.27)
						Hospital LOS (days)	9 (SD 4.26)	7 (SD 3.34)	MD 2.0 (0.4 to 3.6)
Viana-Rojas	Mexico 2023	Prospective Cohort Cardiac ICU	Day 1 VExUS ≥ 1	Patients aged 18–99 years, with a diagnosis of acute coronary syndrome admitted for a hospital stay longer than 24 h	77	AKI (30 Days)	14/31	5/46	OR 6.75 (2.10 to 21.70)
						Mortality (In Hospital)	5/31	3/46	OR 2.76 (0.61to 12.50)
						RRT (Hospital Discharge)	5/31	0/46	OR 19.30 (1.03 to 362.96)
						Hospital LOS (days)	4 (SD 2. 22)	4 (2.22)	MD 0 (1.01 to 1.01)
Bitar	Kuwait 2023	Prospective Cohort General ICU	Day 1 VExUS ≥ 2	Patients ≥ 18y with suspicion of cardiorenal syndrome admitted to a CCU with sepsis	33	RRT (No date range)	7/17	4/16	OR 2.1 (0.47 to 9.30)
Li	China 2024	Prospective Cohort Cardiac Surgery ICU	Day 1 VExUS ≥2	Patients ≥ 18y who underwent elective cardiac surgery	19	AKI (7 Days)	14/33	39/197	OR 2.99 (1.38 to 6.47)
Rihl	Brazil 2023	Prospective Cohort General ICU	Day 1 VExUS ≥ 2	Patients ≥ 18y with non-elective ICU admission and severe AKI	90	Mortality (28 days)	16/36	27/54	OR 0.80 (0.34 to 1.87)
						Hospital LOS (days)	32 (SD 20.15)	42 (SD 24.15)	MD -10.00 (-19.21 to -0.79)
						ICU LOS (days)	19.5 (13.93, 25.07)	21 (17.00, 25.00)	MD -1.50 (-8.35 to 5.35)
						RRT (28 days)	18/36	26/54	OR 1.08 (0.46 to 2.50)
Utrilla-Alvarex	Mexico 2023	Prospective Cohort Cardiac Surgery ICU	Day 1 VExUS ≥ 2	Adult patients (≥ 18y) admitted to critical care unit following cardiac surgery	60	AKI (unknown timing)	15/26	6/34	OR 6.36 (1.96 to 20.63)
						ICU LOS (days)	3 (SD 1.48)	2.5 (SD 0.74)	MD 0.50 (0.12 to 1.12)
						Hospital LOS (days)	14 (SD 8.89)	8 (SD 2.96)	MD 6.00 (2.44 to 9.56)
						Mortality (In Hospital)	2/26	1/34	OR 2.75 (0.24 to 32.10)
						RRT (unknown timing)	1/26	1/34	OR 1.32 (0.08 to 22.15)

Beaubien-Souligny	Canada 2023	Prospective Cohort General ICU	Day 1 VExUS ≥ 2	Patients (≥ 18y) admitted to ICU with severe AKI (KDIGO)	125	RRT (30 Days)	16/30	56/83	OR 0.55 (0.24 to 1.29)
						Mortality (30 Days)	13/30	27/83	OR 1.59 (0.67 to 3.73)
Prager	Canada 2023	Prospective Cohort General ICU	Day 1 VExUS ≥ 2	Patients (≥ 18y) with septic shock (Sepsis-3) and hypotension requiring vasoactive medications and end-organ dysfunction	75	AKI (30 Days)	5/14	30/61	OR 0.57 (0.17 to 1.91)
						RRT (30 Days)	4/14	6/61	OR 3.67 (0.87to 15.37)
						Mortality (30 Days)	3/14	17/61	OR 0.71 (0.18 to 2.85)
						ICU LOS (days)	7.6 (SD 6.22)	6.1 (SD 7.33)	MD 1.50 (-2.24 to 5.24)

ICU = Intensive Care Unit; VExUS = Venous Excess Ultrasound Score; AKI = Acute Kidney Injury; RRT = Renal Replacement Therapy; LOS = Length of Stay; SD = Standard Deviation; MD = Mean Difference; OR = Odds Ratio; CI = Confidence Interval; CCU = Coronary Care Unit; KDIGO = Kidney Disease: Improving Global Outcomes; Sepsis-3 = Third International Consensus Definition for Sepsis.

Figure 1. PRISMA Diagram

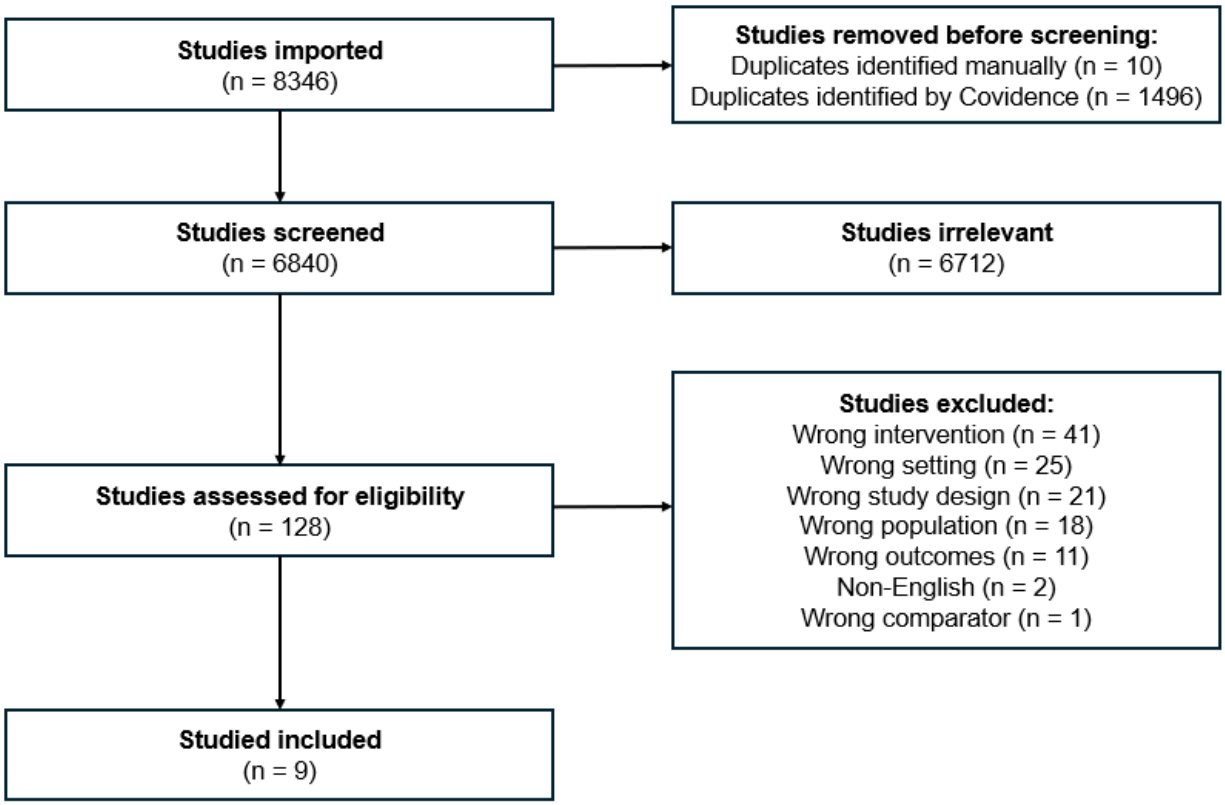
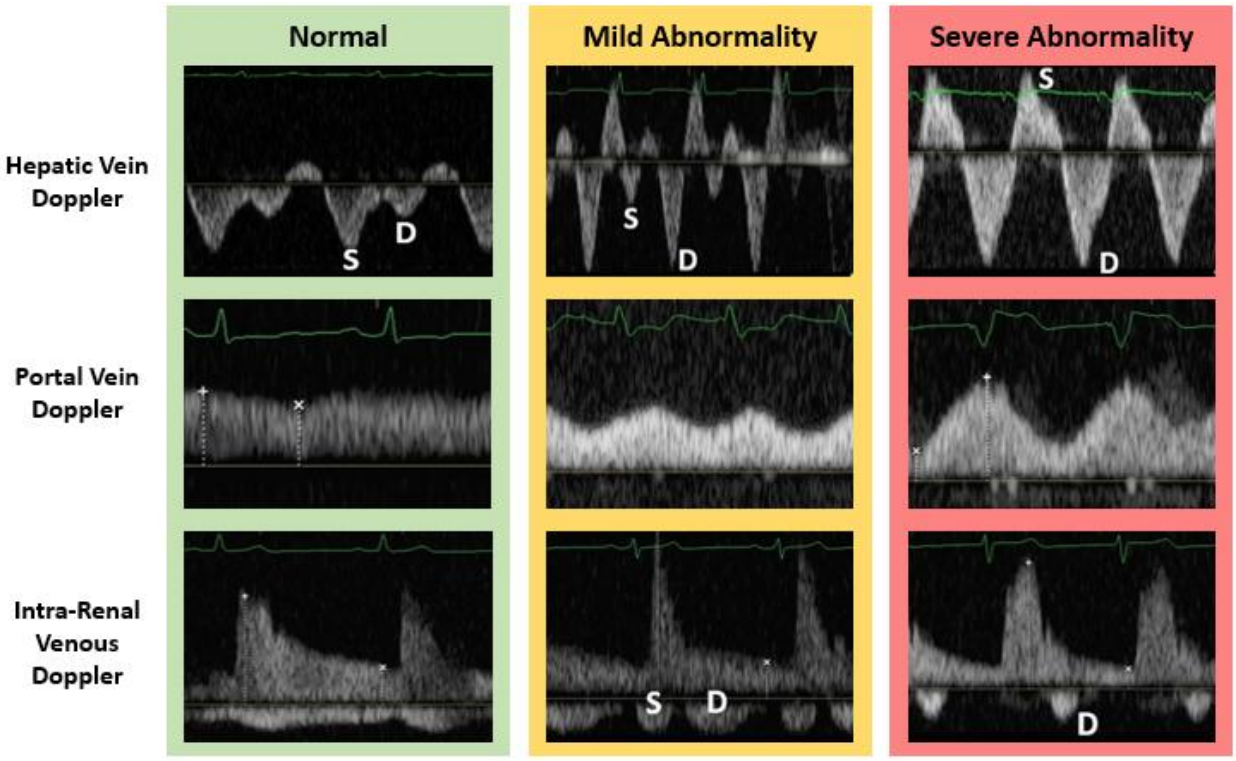


Figure. 2 VEXUS Score Diagram



Grade 0	Grade 1	Grade 2: Mild Congestion	Grade 3: Severe Congestion
IVC < 2 cm	IVC ≥ 2 cm Normal patterns or any mild abnormality pattern	IVC > 2 cm Severe abnormalities in at least one pattern	IVC > 2 cm Severe abnormalities in multiple patterns

Figure. 3 Association between venous congestion and AKI

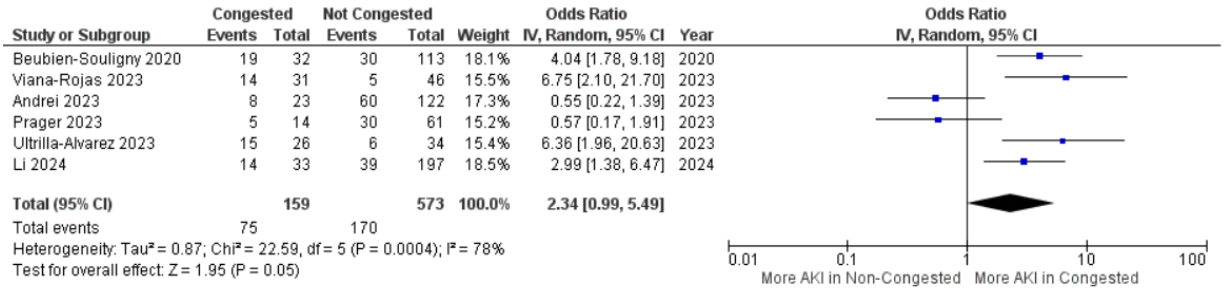


Figure. 4 Association between venous congestion and RRT

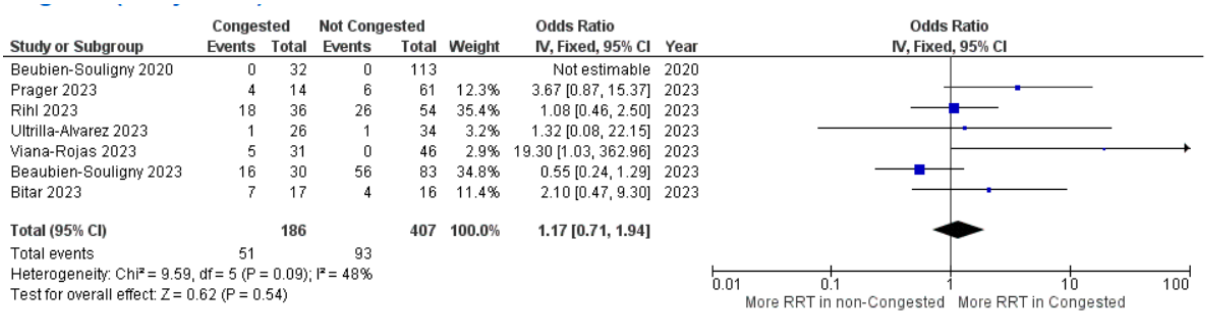


Figure. 5 Association between venous congestion and Mortality

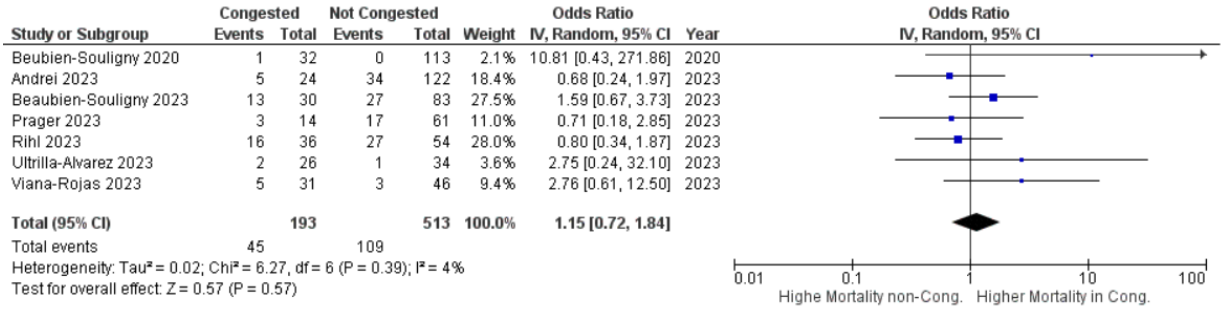


Figure. 6 Association between venous congestion and ICU LOS (days)

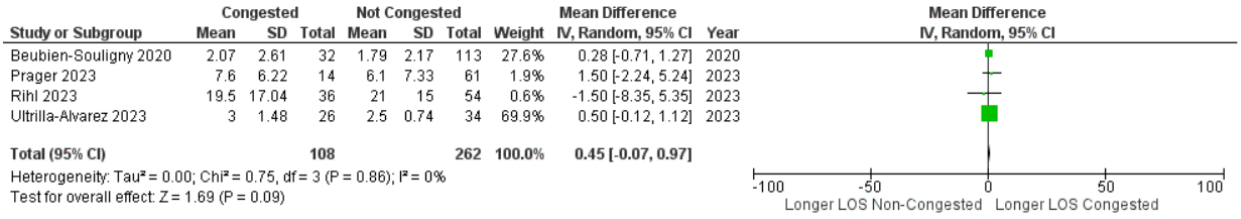


Figure. 7 Association between venous congestion and Hospital LOS (days)

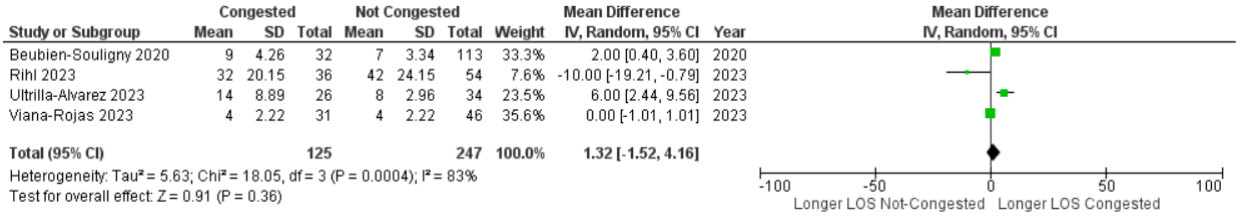
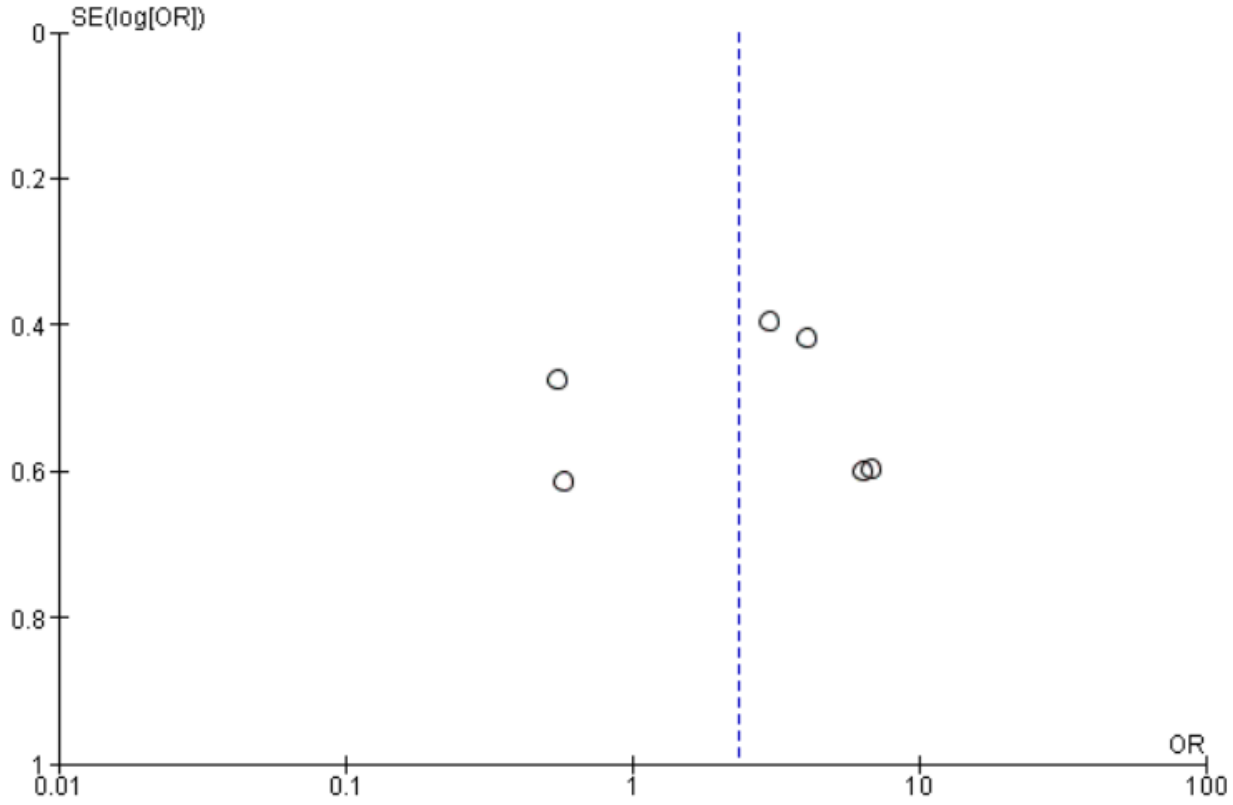


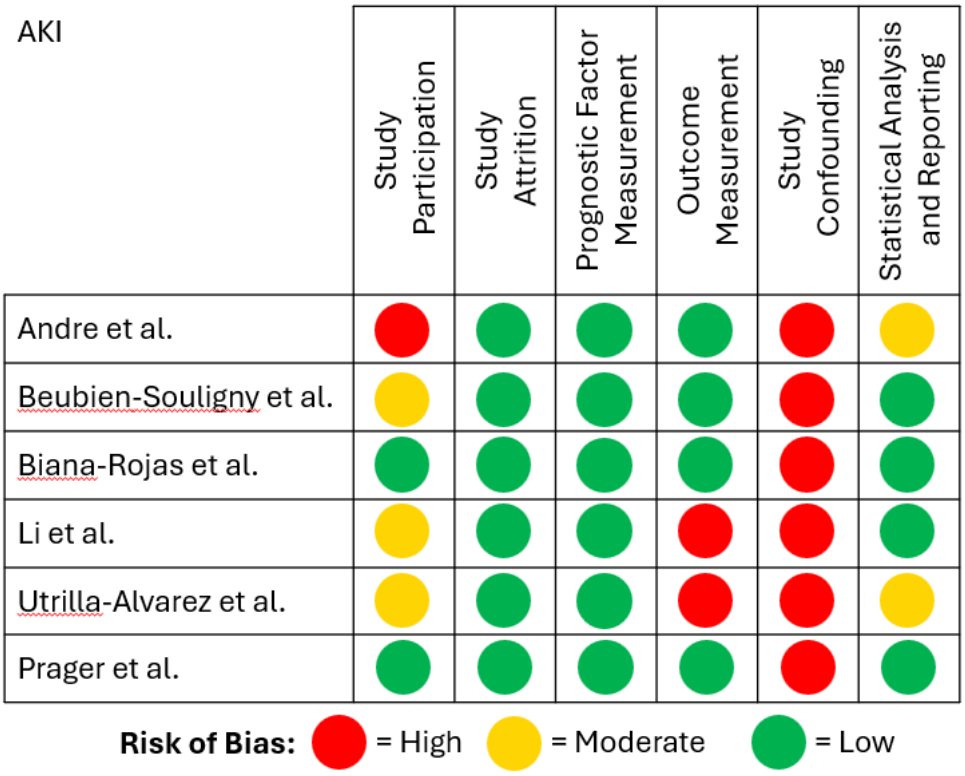
Figure 8. Publication bias for AKI



Caption

Funnel plot of comparison: 1 Congestion, outcome: 1.1 AKI.

Figure 9. QUIPS Risk of Bias for AKI



Appendices

Appendix 1. Search strategy

The following search was conducted in Medline (Ovid) and was adapted for use in other databases.

((Acute Kidney Injury/di,dg,et OR Hepatic Veins/dg OR exp Heart Failure/dg OR exp Liver Failure/dg OR Kidney/dg OR Liver/dg OR (kidney ADJ2 congest*).tw,kf OR (liver ADJ2 congest*).tw,kf OR “renal congestion”.tw,kf OR “hepatic congestion”.tw,kf OR “congestive hepatopathy”.tw,kf OR “cardiac cirrhosis”.tw,kf OR “cardiorenal syndorm*”.tw,kf OR (cardiac ADJ3 kidney dysfunction).tw,kf OR “acute kidney injury”.tw,kf OR AKI.tw,kf

AND

(Central Venous Pressure/ OR Hyperemesis/ OR OR Portal Vein/dg OR CVP.tw,kf OR "venous congestion".tw,kf OR "venous excess".tw,kf OR "organ congestion".tw,kf OR "portal vein pulsatility".tw,kf OR PVPi.tw,kf OR "hepatic vein systolic flow reversal".tw,kf OR "hepatic vein systolic blunting".tw,kf OR "renal resistive index".tw,kf OR "renal venous stasis index".tw,kf OR RVSI.tw,kf OR vein*.tw,kf "venous impedance index".tw,kf)

AND

(exp Echocardiography/ OR Ultrasonography/ OR Ultrasonography, Interventional/ OR exp Ultrasonography, Doppler/ OR Diagnostic Imaging/ OR doppler*.tw,kf OR ultrasound*.tw,kf OR POCUS.tw,kf OR TEE.tw,kf OR echocardio*.tw,kf OR echo.tw,kf OR "diagnostic imaging".tw,kf)

NOT

(exp Child/ OR exp Infant/ OR exp Pediatrics/ OR child* OR pediatric* OR infant*))

Appendix 2. QUIPS with study-specific signaling questions

Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of Reporting (yes, partial, no, unsure)**	**Rating of "Risk of Bias" (High, moderate, low)**
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between PF and outcome is different for participants and eligible non-participants)**			
Source of target population	The source population or population of interest is adequately described for: location (e.g. ICU vs OR), diagnosis (e.g. general critical illness, cardiac surgery, septic shock)		Yes	
Methods use to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential biases (e.g. convenience, consecutive, random)		No	
Inclusion and Exclusion Criteria	Inclusion and exclusion criteria are adequate described (e.g. including explicit diagnostic criteria or 'zero time' description)		Yes	
Adequate study participation	There is adequate participation in the study by eligible individuals			
Baseline Characteristics	The base study sample (ie. Individuals entering the study) are adequate described for age, sex, ventilation status, illness severity , history of kidney disease, AKI status at time of Doppler, and presence of cardiac dysfunction (acute or chronic)			
Summary Study population	The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.			
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between PF and outcome are different for competing and non-competing participants)**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate:		Low	

	Low RoB: <5% missing and/or missing outcome is considered MCAR or MAR (based on differences in prognostic factors above) Mod RoB: 5-10% missing data High RoB: >10% missing and/or big differences in baseline characteristics for important prognostic factors.			
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.		Low	
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.		NA	
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics: age, sex, ventilation status, illness severity		NA	
Outcome and prognostic factor information on those lost to follow-up	There are no important differences between key characteristics age, sex, ventilation status, illness severity and outcomes in participants who completed the study and those who did not.		NA	
Study Attrition Summary	Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome			
3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome)**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including threshold of congestion and clear specification of the method of measurement).		Yes	
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).		Yes	
Valid and Reliable Measurement of PF	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.		Yes	
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.		Yes	
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.		Yes	
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.		NA	
PF Measurement Summary	PF is adequately measured in study participants to sufficiently limit potential bias			

4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF)**			
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct		Low	
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).			
Method and Setting of Outcome Measurement	Method and Setting of Outcome Measurement			
Outcome Measurement Summary	Outcome of interest is adequately measured in study participants to sufficiently limit potential bias.			
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**			
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: use of diuretics, dialysis, mechanical ventilation), are measured.			
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).			
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).			
Method and Setting of Confounding Measurements	The methods and setting of confounding measurements are the same for all study participants			
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data			
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g. matching for key variables, stratification, or initial assembly of comparable groups)			
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the analysis (i.e. appropriate adjustments)			
Study Confounding Summary	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between PF and outcome			
6. Statistical	**Goal: To judge the risk of bias related to the statistical**			

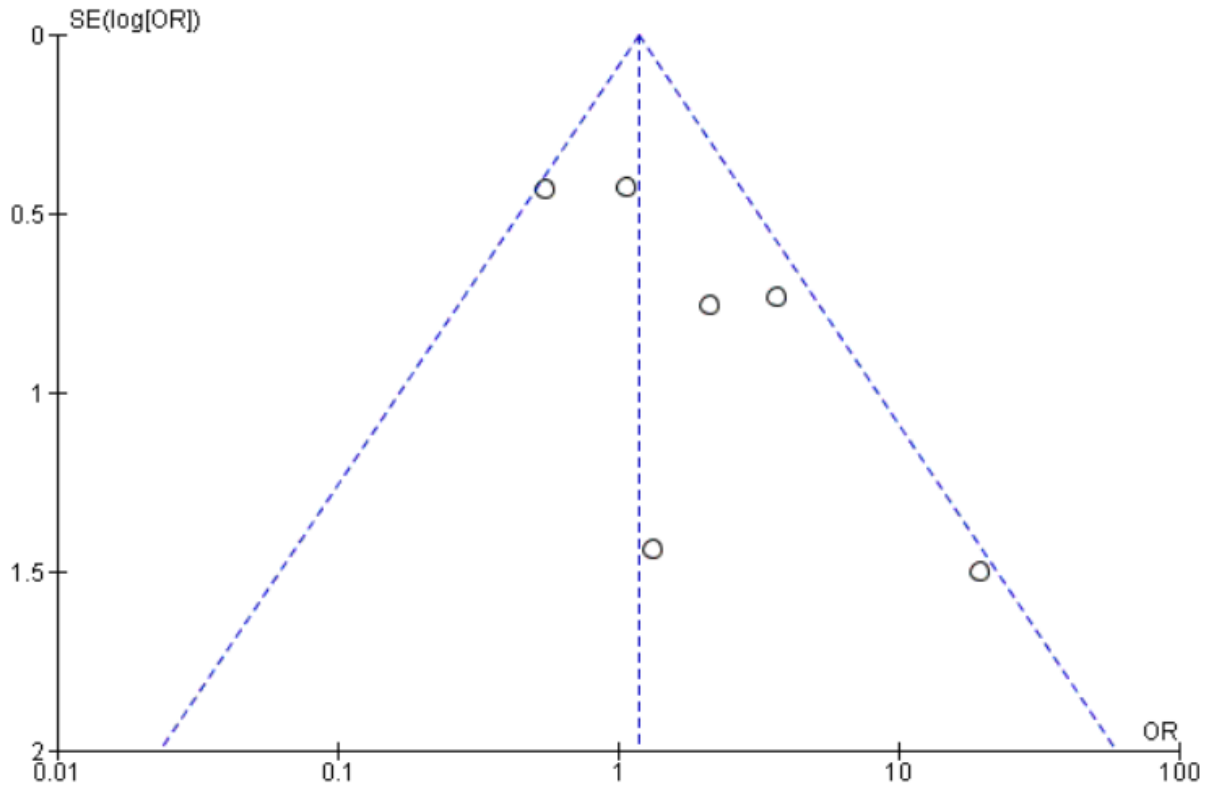
Analysis and Reporting	**analysis and presentation of results**			
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.			
Model Development Strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.			
Model Development Strategy	The selected statistical model is adequate for the design of the study			
Reporting of results	There is no selective reporting of results			
6. Statistical Analysis and Presentation Summary	The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid of spurious results			

Appendix 3. GRADE Summary of Findings table

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VEXUS	Non VEXUS	Relative (95% CI)	Absolute (95% CI)	
AKI (Multiple Follow Ups)											
6	non-randomised studies	serious	serious	not serious	not serious	High magnitude of association increases level of certainty	75/159 (47.2%)	170/573 (29.7%)	**OR 2.34** (0.99 to 2.34)	**200 more per 1,000** (from 2 fewer to 200 more)	◯⊕◯◯ low
RRT (FOLLOW UP 28 DAYS)											
7	non-randomised studies	serious	serious	not serious	not serious	none	51/186 (27.4%)	93/407 (22.9%)	**OR 1.17** (0.71 to 1.94)	**29 more per 1,000** (from 55 fewer to 136 more)	⊕◯◯◯ Very low
MORTALITY (FOLLOW UP 28 DAYS)											
7	non-randomised studies	serious	serious	not serious	not serious	none	45/193 (23.3%)	109/513 (21.2%)	**OR 1.15** (0.72 to 1.84)	**24 more per 1,000** (from 50 fewer to 119 more)	⊕◯◯◯ Very low
ICU LOS											
4	non-randomised studies	serious	serious	not serious	not serious	none	108	262	-	MD **0.45 days higher** (0.07 lower to 0.97 higher)	⊕◯◯◯ Very low
Hospital LOS											
4	non-randomised studies	serious	serious	not serious	not serious	none	125	247	-	MD **1.32 days higher** (1.52 lower to 4.16 higher)	⊕◯◯◯ Very low

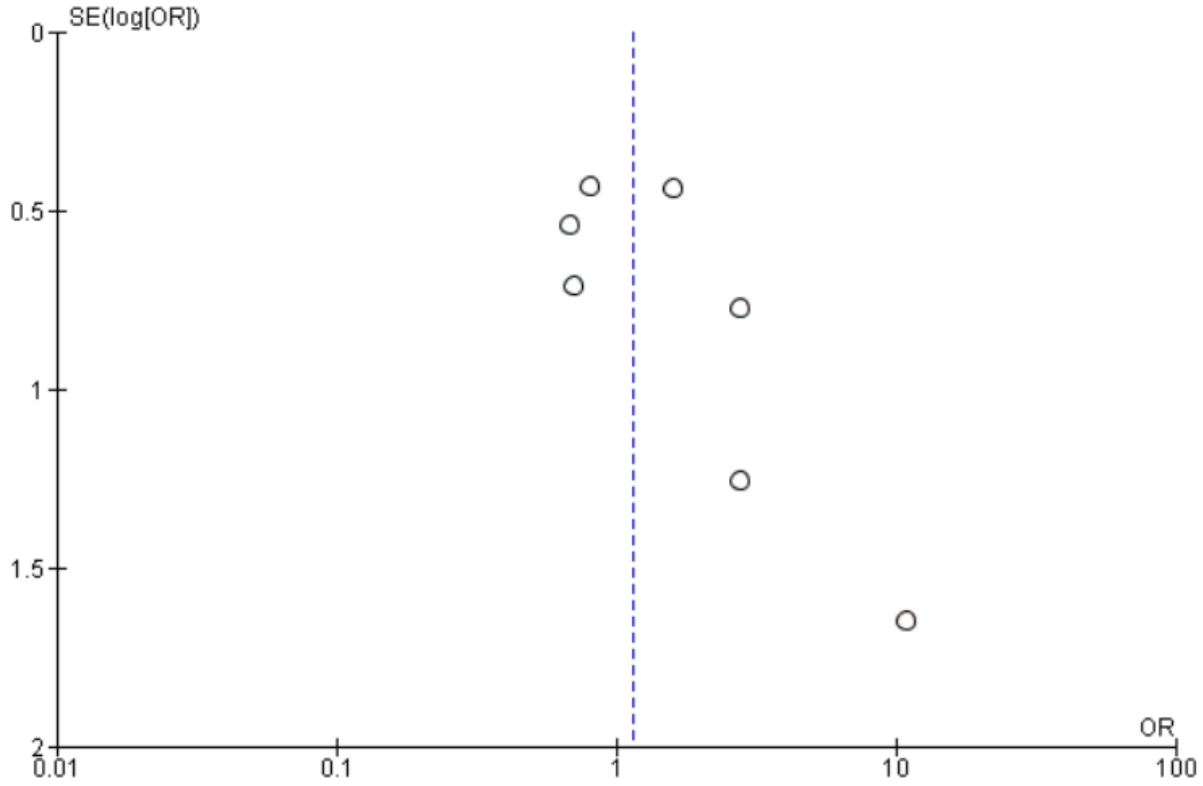
CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Appendix 4. Funnel plots for RRT, mortality, ICU LOS, and hospital LOS



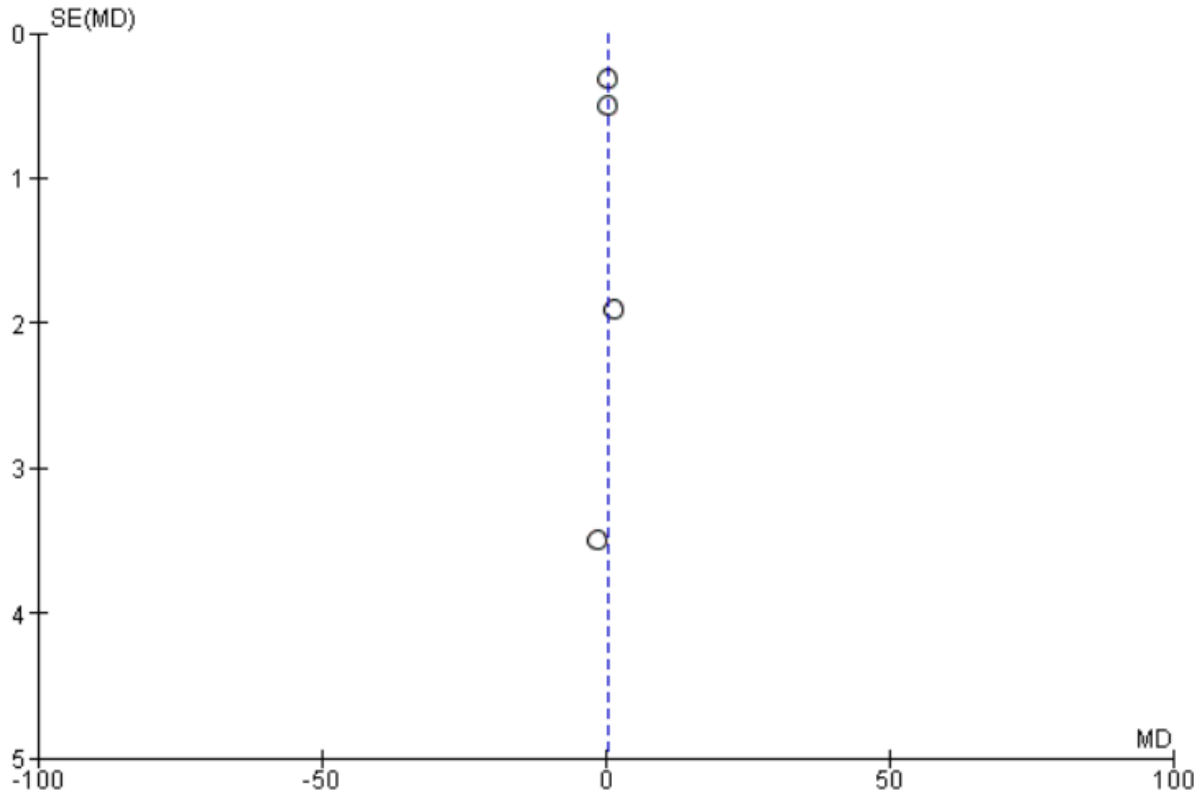
Caption

Funnel plot of comparison: 1 Congestion, outcome: 1.2 RRT.



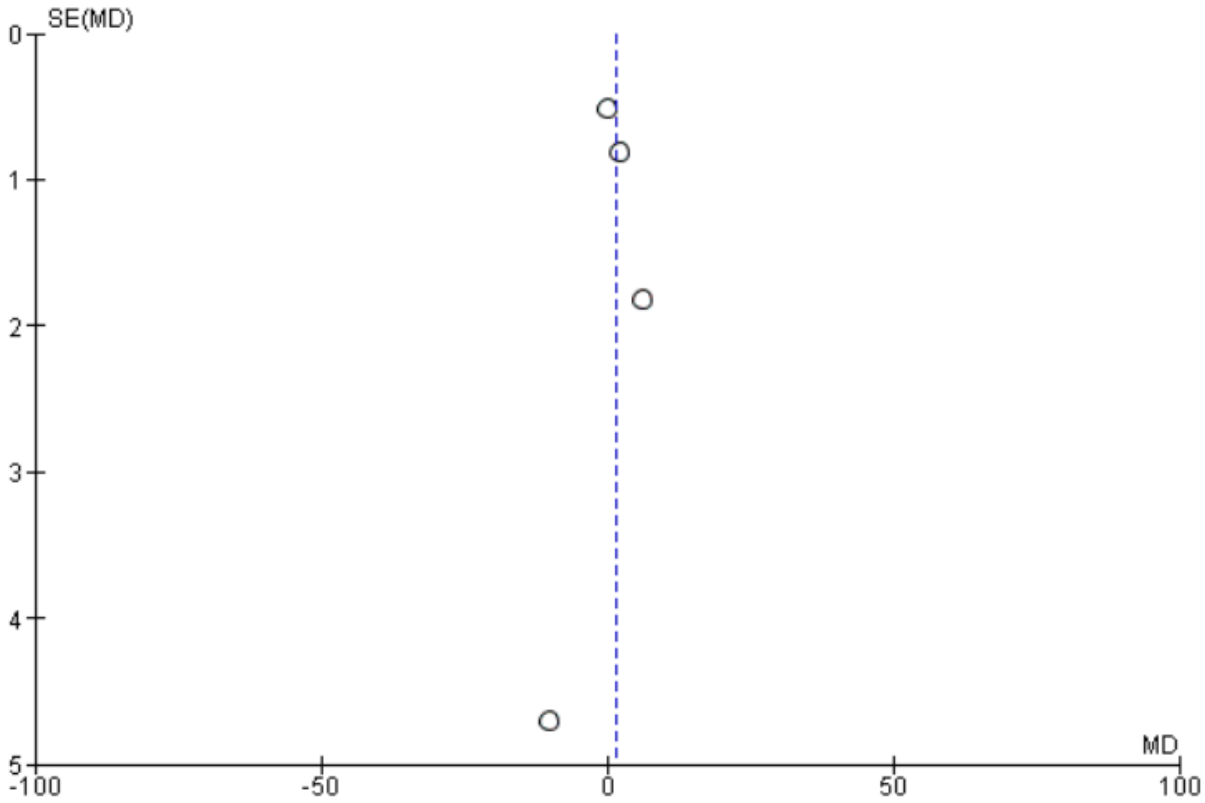
Caption

Funnel plot of comparison: 1 Congestion, outcome: 1.3 Mortality.



Caption

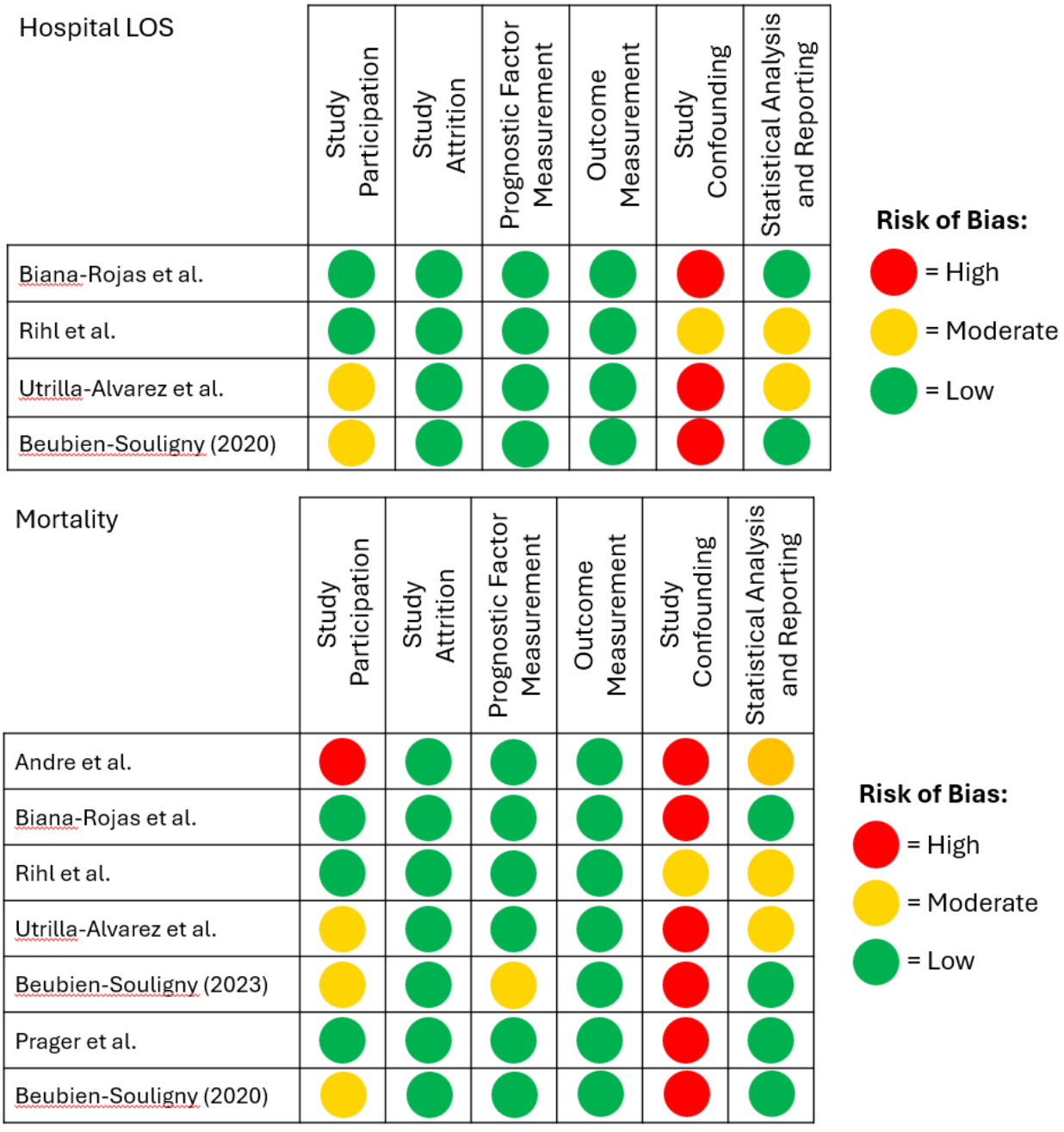
Funnel plot of comparison: 1 Congestion, outcome: 1.4 ICU LOS.



Caption

Funnel plot of comparison: 1 Congestion, outcome: 1.5 Hospital LOS.

Appendix 5. QUIPS risk of bias tables for RRT, mortality, ICU LOS, and hospital LOS



RRT

	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting
Biana-Rojas et al.	Low	Low	Low	Low	High	Low
Bitar et al.	High	Low	Low	High	High	High
Rihl et al.	Low	Low	Low	Low	Moderate	Low
Utrilla-Alvarez et al.	Moderate	Low	Low	High	High	Moderate
Beubien-Souligny (2023)	Moderate	Low	Moderate	Low	High	Low
Prager et al.	Low	Low	Low	Low	High	Low
Beubien-Souligny (2020)	Moderate	Low	Low	Low	High	Low

Risk of Bias:

= High

= Moderate

= Low

ICU LOS

	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting
Rihl et al.	Low	Low	Low	Low	Moderate	Moderate
Utrilla-Alvarez et al.	Moderate	Low	Low	Low	High	Moderate
Prager et al.	Low	Low	Low	Low	High	Low
Beubien-Souligny (2020)	Moderate	Low	Low	Low	High	Low

Risk of Bias:

= High

= Moderate

= Low

MANUSCRIPT #2 – Pilot Study (In Review – Journal of Clinical Medicine)

Article

The VTI-VeXUS index in septic shock: An exploratory proof-of-concept observational study of a novel hemodynamic parameter

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Abstract

Aim: Both the arterial and venous systems independently predict mortality in septic shock, yet no bedside tools integrate their assessment. Risk stratification becomes challenging when arterial parameters suggest favorable outcomes while venous parameters indicate poor prognosis, or vice versa. To address this gap, we developed the VTI-VeXUS index and conducted this proof-of-concept study to test its association with mortality. Methods: We conducted a prospective cohort study in two ICUs, enrolling adult patients with septic shock. We calculated the VTI-VeXUS index (VTI/[VeXUS+1]) from ultrasound measurements obtained within 24 hours of ICU admission and stratified patients as high and low VTI-VeXUS index based on a cutoff of 11. We evaluated the primary outcome of mortality at 30 days using survival analysis. Results: We enrolled 62 patients. Patients with low VTI-VeXUS index had higher rates of left ventricular dysfunction (32.3% vs. 3.2%, $p = 0.006$), right ventricular dysfunction (35.5% vs. 0.0%, $p < 0.001$), lower stroke volume (54.0 mL vs. 62.0 mL, $p = 0.005$), and increased 30-day mortality (HR 3.83, 95% CI 1.25–11.78). Conclusion: In this exploratory proof-of-concept study, a low VTI-VeXUS index was associated with ventricular dysfunction and increased mortality. While limited by small sample size and univariate analysis, these findings suggest this novel integrated metric warrants validation in larger prospective studies.

.

Keywords: Sepsis, Hemodynamics, Venous Congestion, Ultrasound, Critical Care

1. Introduction

Despite numerous care initiatives, the morbidity and mortality from septic shock remain high [1]. Historically, early resuscitation efforts have aimed to improve oxygen delivery to tissues by optimizing the arterial system, augmenting preload via fluid administration, enhancing contractility with inotropes, and increasing arterial systemic vascular resistance using vasoactive medications [2, 3]. These arterial parameters, particularly cardiac output and stroke volume, have substantial prognostic value in septic shock.

Emerging literature has identified the venous system as a crucial determinant of outcomes in septic shock [4]. Specifically, venous congestion is a critical factor contributing to organ dysfunction and mortality [5-7]. Venous congestion develops when elevated right atrial pressure transmits retrograde to the liver, brain, kidneys, and other end organs [6, 8-10]. Venous congestion increases tissue afterload; even modestly elevated pressures (e.g., right atrial pressure of 12 mmHg) impair tissue perfusion [11]. Tools such as the Venous Excess Ultrasound Score (VeXUS) now allow bedside quantification of this congestion and are independently associated with adverse patient outcomes.

Although both arterial and venous parameters independently predict mortality in septic shock, their combined prognostic significance remains unexplored. Clinicians particularly need guidance when these systems diverge; when one appears reassuring while the other signals deterioration. Does a patient with preserved cardiac output but severe congestion have a better prognosis than one with low cardiac output but no congestion? When both systems are compromised, is mortality risk additive or synergistic? Without understanding these relationships, clinicians cannot accurately assess risk or prioritize interventions.

Similar to how the shock index (a simple ratio of heart rate to systolic blood pressure) enhances early detection of hemodynamic compromise by combining heart rate and blood pressure,

integrating arterial and venous ultrasound parameters may identify high-risk states not apparent when considering each parameter separately. Building on our prior work, we propose the novel VTI-VeXUS index—the first metric to combine left ventricular outflow tract (LVOT) velocity time integral (VTI), a surrogate for the arterial system, with the Venous Excess Ultrasound Score (VeXUS), a surrogate for the venous system. Like the shock index, this value could facilitate rapid bedside risk stratification when individual parameters suggest conflicting prognostic outlooks.

This exploratory study represents the initial proof of concept for the VTI-VeXUS index in septic shock. By combining left ventricular outflow tract VTI with VeXUS measurements, we aim to determine whether this integrated metric provides prognostic value. If lower VTI-VeXUS indexes are associated with increased mortality, this would justify larger studies to quantify the index's prognostic accuracy and establish optimal thresholds for clinical decision-making.

2. Materials and Methods

Ethics Approval

This study was approved by the Western University Research Ethics Board (WREM Approval #120202). We obtained consent from all patients or their substitute decision-makers using a deferred consent model. This approach enabled the inclusion of critically ill patients who were unable to provide consent at the time of enrollment.

Study Reporting

The study was designed and reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [12].

Study Design and Setting

We conducted a prospective, multicentre observational cohort study in two tertiary intensive care units (ICUs) in London, Ontario, Canada. These ICUs care for medical-surgical, transplant, trauma, and neurological patients and together provide 64 critical care beds. A dedicated critical care ultrasound service performed focused echocardiograms and VeXUS measurements.

Participants

We enrolled adult patients (≥18 years old) diagnosed with septic shock based on Sepsis-3 criteria within 12 hours of ICU admission. Additional inclusion criteria included at least one feature of

end-organ dysfunction: serum lactate ≥2.0 mmol/L, acute kidney injury (AKI) of at least Acute Kidney Injury Network Stage I, Glasgow Coma Scale (GCS) <13, or the need for mechanical ventilation. We excluded patients with limitations on life support interventions, those who had undergone liver transplantation, or those with pre-existing end-stage renal disease requiring dialysis.

Ultrasound Measurements

Trained operators performed ultrasound measurements; these operators had fellowship training in critical care ultrasound and completed specific training in VeXUS. This training consisted of a one-hour didactic session addressing the use of VeXUS, followed by direct supervision for the first three scans to ensure competency. Ultrasound assessments included evaluations of the inferior vena cava, hepatic, portal, and intra-renal veins within 24 hours of ICU admission.

Possible VeXUS scores range from 0 to 3. Scores of 0 or 1 represented 'no congestion,' and scores of 2 or 3 represented moderate to severe 'congestion' [7]. We assessed left ventricular (LV) and right ventricular (RV) function and dichotomized findings into normal or abnormal. We defined LV dysfunction as an ejection fraction of less than 50% qualitatively. Similarly, we defined RV dysfunction qualitatively and based on semi-quantitative measurements such as the tricuspid valve s' (TV S') velocity or tricuspid annular plane systolic excursion (TAPSE). We assessed the severity of tricuspid valve regurgitation using colour Doppler, with moderate and severe tricuspid regurgitation grouped for analyses. We estimated the stroke volume using the LVOT VTI and the LVOT diameter.

We calculated the VTI-VeXUS index by dividing the LVOT VTI by the VeXUS score plus 1 (VTI/[VeXUS+1]). We added 1 to the VeXUS score before calculating the index to prevent undefined values resulting from division by zero.

Data Collection

Trained research assistants collected data from both paper and electronic health records. We entered information describing demographics, clinical characteristics, ultrasound measurements, and patient outcomes into a REDCap (Research Electronic Data Capture) database. To ensure accuracy, outcome data were reviewed in duplicate by a study investigator blinded to the patient's congestion status and echocardiographic data.

Sample Size Justification

We powered this proof-of-concept study to detect an unadjusted hazard ratio of 3.5 for 30-day mortality between patients with high versus low VTI-VeXUS index. Although this represents a large effect size, three considerations justified this approach. First, unadjusted estimates typically attenuate after covariate adjustment; starting with a sizeable effect maximizes the likelihood that a clinically relevant signal will remain once we undertake an adjusted analysis in the next phase of this research program. Second, the prognostic strength of related physiological constructs already demonstrates effects in this range: moderate to severe venous congestion (VeXUS grade 2-3) [13, 14] and left ventricular dysfunction each independently carry a hazard ratio of 3 to 4 for mortality [15-17]. For our new index to add clinical value, it must at minimum rival or exceed

these established benchmarks. Based on a two-sided alpha of 0.05, a beta coefficient of 0.20, a hazard ratio of 3.5, and a mortality rate of 30-35% at 30 days, we require at least 60 participants.

Data Analysis

We analyzed data using R (version 4.4.1). To stratify patients into low and high VTI-VeXUS index groups, we dichotomized patients using a VTI-VeXUS index cutoff of 11, based on a physiologic framework inspired by Diamond-Forrester hemodynamic profiling [18]. This framework categorizes patients by arterial flow (normal VTI: >20-22 cm) and venous congestion (moderate to severe congestion: VeXUS score 2-3; no to mild venous congestion: VeXUS score 0-1). A normal profile, defined as a definitively normal stroke volume (VTI 22 or higher) with no or mild congestion (VeXUS 0 or 1), yields an index of at least 11 (VTI of 22 divided by VeXUS ≤1 plus 1). We selected 11 as the cutoff, representing a value that corresponds with normal hemodynamic coupling as well as the median value in the data.

We then compared baseline characteristics, demographics, comorbidities, clinical data, echocardiographic features, and outcomes. We summarized categorical variables as counts and percentages and continuous variables as medians with interquartile range (IQR), given that the data were not normally distributed. We used the Wilcoxon Rank Sum Test to compare differences in continuous data and the Chi-square or Fisher's exact test to compare differences in categorical data. We used Cox proportional hazards models to perform unadjusted analyses of the relative hazard of 30-day mortality. We used univariate linear and logistic regression models to determine the association between VTI-VeXUS index and secondary outcomes, including major adverse kidney events (MAKE) at 30 days (a composite of persistent creatinine elevation of >200%

baseline, dialysis, or death at 30 days), renal replacement therapy (RRT) at 30 days, duration of vasoactive agents, duration of mechanical ventilation, and ICU length of stay. We generated survival curves using the Kaplan-Meier method. All p-values were two-sided, with statistical significance defined as $p < 0.05$.

3. Results

We screened 350 patients for eligibility between January 1, 2022, and January 1, 2023. Of those, we included 62 patients in the study.

Baseline Characteristics

The median age was 64.0 years (IQR 56.0 to 73.0), and 37 (59.7%) patients in the cohort were female. The median VTI-VeXUS index was 11.4 (IQR 7.6 to 17.07). Between the high and low VTI-VeXUS index groups, we found no significant differences in age, sex, or severity of illness score as defined by the multiorgan dysfunction score (MODS), or comorbidities. The primary source of sepsis was pulmonary in 83.9% of patients, with a higher frequency in the high VTI-VeXUS group (96.8% vs. 71.0%, $p = 0.016$). Intra-abdominal sources of sepsis were also more common in the high VTI-VeXUS group compared to the low VTI-VeXUS group (29% vs. 3.2%, $p = 0.016$). Table 1 summarizes patient demographics.

Between the high and low VTI-VeXUS groups, we also found no differences in mean arterial pressure at admission, heart rate, or vasopressor doses at the time of ICU admission. Moreover, we found no difference in the use of inotropes, positive pressure ventilation, fluid balance pre-VeXUS, or laboratory data at the time of ICU admission (lactate, creatinine, white blood cells, platelets, or hemoglobin). Table 2 summarizes clinical variables and laboratory data.

Table 1. Patient demographics for Low and High VTI-VEXUS Index

Demographic Variables	Overall, N = 62[1]	High VTI-VEXUS Index N = 31[1]	Low VTI-VEXUS Index N = 31[1]	p-value[2]
Age (Q1, Q3)	64.0 (56.0, 73.0)	64.0 (56.0, 73.0)	63.0 (54.0, 72.5)	0.9
Male n (%)	25 (40.3%)	11 (35.5%)	14 (45.2%)	0.6
Body Mass Index (kg/m^2)	26.7 (21.2, 33.1)	27.0 (23.6, 34.1)	25.6 (20.2, 31.9)	0.4
MODS (IQR)	4.0 (3.0, 6.0)	4.0 (2.0, 6.0)	5.0 (3.3, 8.0)	0.14
Comorbidities, n(%)				
CHF	3 (4.8%)	2 (6.5%)	1 (3.2%)	>0.9
CAD	7 (11.3%)	1 (3.2%)	6 (19.4%)	0.1
CKD	3 (4.8%)	1 (3.2%)	2 (6.5%)	>0.9
Stroke	3 (4.8%)	3 (9.7%)	0 (0.0%)	0.2
Cirrhosis	1 (1.6%)	0 (0.0%)	1 (3.2%)	>0.9
COPD	8 (12.9%)	5 (16.1%)	3 (9.7%)	0.7
Atrial Fibrillation	7 (11.3%)	2 (6.5%)	5 (16.1%)	0.4

Diabetes	14 (22.6%)	8 (25.8%)	6 (19.4%)	0.8
Source of Sepsis				
Pulmonary	52 (83.9%)	30 (96.8%)	22 (71.0%)	0.016
Intraabdominal	10 (16.1%)	1 (3.2%)	9 (29.0%)	0.016
[1] Median (IQR); n (%)				
[2] Wilcoxon rank sum test; Fisher's exact test; Welch Two Sample t-test; Pearson's Chi-squared test				
Abbreviations: *MODS*: Multi-organ dysfunction score; *CKD*: Chronic Kidney Disease; *COPD*: Chronic Obstructive Pulmonary Disease; *CHF*: Congestive Heart Failure; *CAD*: Coronary Artery Disease; *Afib*: Atrial fibrillation				

Echocardiographic Data

Patients with a low VTI-VeXUS index had higher rates of RV dysfunction (35.5% vs. 0%, $p < 0.001$) and LV dysfunction (32.3% vs. 3.2%, $p = 0.006$). Patients with a low VTI-VeXUS index also had reduced stroke volumes (54.0 mL vs. 62.0 mL, $p = 0.005$), reduced VTI (16.0 cm vs. 18.2 cm, $p = 0.003$), and reduced TV S' (12 vs. 14.2 cm/second, $p = 0.027$). However, we found no differences in cardiac output, TAPSE, or frequency of moderate to severe TR between the two groups.

Table 2. Clinical Variables for Patients with High and Low VTI-VEXUS Index

Clinical Variables	Overall, N = 62[1]	High VTI-VEXUS Index, N = 31[1]	Low VTI-VEXUS Index, N = 31[1]	p-value[2]
Initial MAP (mmHg)	70.5 (64.3, 84.0)	70.0 (65.0, 87.5)	71.0 (64.0, 80.5)	0.6
Initial HR (bpm)	93.0 (82.3, 111.5)	90.0 (81.5, 104.5)	99.0 (84.0, 110.0)	0.3
Highest Vasopressor dose (NE equivalents) on day 1 (mcg)	21.2 (8.3, 30.0)	20.0 (8.0, 30.4)	22.0 (11.0, 28.9)	0.6
Use of inotropes day 1	10 (16.1%)	3 (9.7%)	7 (22.6%)	0.3
Positive Pressure Ventilation at time of POCUS day 1	40 (64.5%)	16 (51.6%)	24 (77.4%)	0.063
Fluid balance before day 1 VEXUS	1,112.0 (425.0, 3,434.0)	1,000.0 (225.0, 3,280.0)	1,533.0 (628.5, 3,264.5)	0.3
Laboratory Data				

Lactate, mmoL/L	2.2 (1.6, 4.0)	1.9 (1.3, 3.3)	3.1 (1.9, 4.1)	0.075
Baseline Creatinine, umol/L	93.0 (65.5, 107.0)	94.0 (71.5, 107.0)	92.0 (61.0, 107.0)	0.5
WBC	17.0 (10.0, 26.0)	14.0 (9.0, 23.5)	17.5 (11.3, 27.5)	0.4
Hemoglobin, g/dL	103.5 (86.8, 123.8)	108.0 (88.5, 123.5)	103.0 (87.5, 124.5)	0.7
Platelets	214.5 (137.0, 273.5)	217.0 (120.0, 277.0)	212.0 (144.0, 265.5)	0.6
[1] Median (IQR); n (%)				
[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Welch Two Sample t-test				
Abbreviations: MAP: Mean Arterial Pressure; HR: Heart Rate; NE: Norepinephrine equivalents; POCUS: Point of care ultrasound				

Table 3. Echocardiographic data for patients with high and low VTI-VEXUS

Echocardiography Variables	Overall, N = 62[1]	High VTI-VEXUS Index, N = 31[1]	Low VTI-VEXUS Index, N = 31[1]	p-value[2]
LV dysfunction	11 (17.7%)	1 (3.2%)	10 (32.3%)	0.006
RV dysfunction	11 (17.7%)	0 (0.0%)	11 (35.5%)	<0.001
RV dilation	19 (30.6%)	4 (12.9%)	15 (48.4%)	0.006
Moderate or Severe TR	8 (13.1%)	2 (6.7%)	6 (19.4%)	0.3
VTI (cm)	17.1 (15.3, 19.8)	18.2 (16.7, 21.1)	16.0 (13.9, 18.9)	0.003
Stroke volume (mL)	58.0 (50.4, 67.0)	62.0 (55.0, 70.0)	54.0 (47.0, 65.2)	0.005
Cardiac Output (L/min)	5.3 (4.1, 6.0)	5.4 (4.7, 6.4)	5.1 (3.5, 5.6)	0.088
TAPSE (mm)	21.8 (17.9, 24.8)	21.7 (18.8, 24.4)	22.0 (16.6, 24.9)	>0.9
TV S' (cm/s)	13.4 (10.8, 15.1)	14.2 (12.4, 15.7)	12.0 (8.9, 14.5)	0.027

[1] n (%); Median (IQR)

[2] Fisher's exact test; Pearson's Chi-squared test; Welch Two Sample t-test; Wilcoxon rank sum test

Patient Outcomes

Patients with a low VTI-VeXUS index demonstrated an increased hazard of death at 30 days (HR 3.83, 95% CI: 1.25 to 11.78) compared to patients with a high index (Table 4). Patients with a high VTI-VeXUS index also demonstrated increased survival compared to patients with a low VTI-VeXUS index (p = 0.011) (Figure 1). We found no important differences between high and low VTI-VeXUS index groups for MAKE-30 (OR = -0.06, 95% CI: -0.15 to 0.03), initiation of new renal replacement therapy (OR = 0.02, 95% CI: -0.10 to 0.13), duration of vasopressor use (β = -0.03, 95% CI: -0.21 to 0.14), duration of mechanical ventilation (β = -0.1, 95% CI: -0.41 to 0.21), or ICU length of stay (β = -0.25, 95% CI: -0.75 to 0.7) (Table 4).

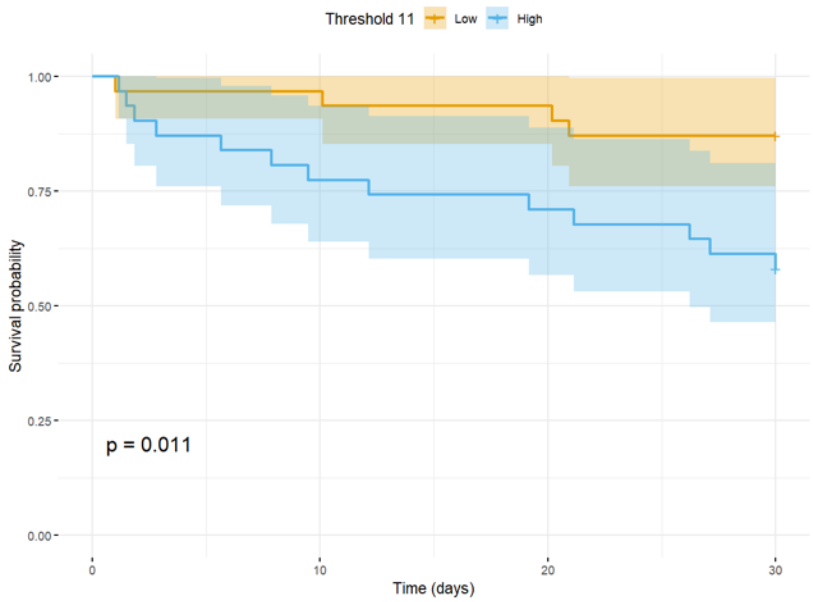

Figure 1. Mortality over 30 days for patients with high or low VTI-VeXUS index

Table 4. Outcomes for patients with high and low VTI VEXUS

Outcome	Analysis	P-value
Primary	Cox Proportional Hazard Model (VTI-VEXUS Threshold < 11)	
30-day mortality	HR 3.83 [1.25 – 11.78]	0.018
Secondary	VTI-VEXUS Index Regression Coefficient (95% CI)	
MAKE-30	OR -0.059 (95% CI -0.151, 0.027)	0.188
New renal replacement therapy start at 30 days	OR 0.017 (95% CI -0.097, 0.132)	0.761
Duration of vasoactive medications, days	β -0.033 (95% CI -0.205, 0.138)	0.703
Duration of mechanical ventilation, days	β -0.099 (-0.409, 0.210)	0.532

ICU length of stay, days	β -0.249 (-0.745, 0.695)	0.946

4. Discussion

In this exploratory proof-of-concept study, we present the first evaluation of the novel VTI-VeXUS index in critically ill patients. Patients with a low VTI-VeXUS index exhibited increased 30-day mortality. While we must interpret these unadjusted results with caution, the magnitude of this effect suggests potential clinical significance that merits further investigation. Despite methodological limitations, these findings indicate that combining arterial flow with venous congestion measurements may capture important physiological derangements in septic shock. Our results warrant validation through larger prospective studies with multivariable adjustment.

In septic shock, arterial parameters such as cardiac output have long been recognized as important predictors of mortality. Consequently, resuscitation paradigms have traditionally focused on optimizing forward flow through the administration of fluids and vasoactive medications. However, recent evidence has established the venous system as an equally important determinant of outcomes. Venous congestion, now quantifiable through tools like the VeXUS score, independently predicts organ failure and mortality. Despite growing recognition that both systems influence outcomes, current practice evaluates them separately. This approach creates clinical uncertainty when arterial and venous parameters portend divergent prognoses. For instance, preserved cardiac output may suggest a favorable outlook, while severe venous congestion indicates high mortality risk. The lack of integrated hemodynamic parameters leaves clinicians without tools to assess the combined impact of arterial and venous dysfunction. Based on our preliminary findings, the VTI-VeXUS index addresses this gap by combining these

complementary measurements into a single metric, capturing hemodynamic information that neither parameter alone can provide.

While our study provides the first evidence for the VTI-VeXUS index in septic shock, other integrated hemodynamic indices have demonstrated similar conceptual value in different populations. For example, the Pulmonary Arterial Pressure Index (PAPi) combines measurements of right ventricular stroke volume surrogate and central venous pressure to identify patients at risk of adverse outcomes. In patients with heart failure, low PAPi is associated with an increased risk of mortality and the need for mechanical circulatory support [19-21]. However, PAPi evaluates only right ventricular function and necessitates invasive pulmonary artery catheterization, limiting its broader use in critical care. The VTI-VeXUS index shares PAPi's biological rationale of integrating arterial and venous hemodynamics but is assessed using non-invasive point-of-care ultrasound.

In our previous work, we outlined a conceptual framework for integrated assessment of arterial and venous systems [22, 23]. The present study provides empirical support for this approach, demonstrating that the VTI-VeXUS index captures stroke volume and venous congestion in a unified physiologic profile. This index offers several distinct advantages: bedside acquisition using widely available ultrasound technology, repeatability for serial monitoring, and applicability across diverse clinical settings. These features enable clinicians to track hemodynamic trajectories and therapeutic responses over time. Moreover, by shifting from isolated assessment of individual systems toward integrated hemodynamic evaluation, the index represents a conceptual advancement in septic shock management. Beyond hemodynamic assessment, the VTI-VeXUS index may enable clinicians to stratify risk, support triage and admission decisions, and tailor monitoring intensity for patients with septic shock. Its non-

invasive nature and ease of use could facilitate broader adoption across various clinical settings. Future studies should prospectively validate the VTI-VeXUS index, clarify optimal thresholds, and determine whether its use improves patient outcomes and guides individualized therapy.

Despite its promise, the VTI-VeXUS index has important limitations. Like the shock index or PAPi, it cannot identify the underlying cause of shock or venous congestion. Conditions such as RV failure, severe tricuspid regurgitation, pericardial effusion, pulmonary hypertension, or biventricular failure can all produce low cardiac output with congestion. Clinicians should interpret a low VTI-VeXUS index as an early warning sign or as a signal to conduct further diagnostic evaluation, not as an instruction to initiate specific therapies such as decongestion or inotrope administration.

This study has several strengths. It is the first to empirically evaluate the VTI-VeXUS index—a novel, non-invasive index integrating arterial and venous physiology in septic shock. We leveraged prospectively collected data, applied standardized ultrasound protocols, and ensured blinded outcome assessment to minimize bias. The VTI-VeXUS index can be obtained rapidly at the bedside using widely available ultrasound technology, supporting scalability and implementation in diverse settings.

This study has several limitations. The small sample size yielded imprecision in the confidence intervals (CI) around our point estimate. Moreover, we enrolled patients at two hospitals, which may limit generalizability. Importantly, our results are unadjusted and remain exploratory as a proof of concept for this novel index; therefore, our effect size may be overestimated. However, this study was designed as a proof of concept to determine whether a signal exists that justifies investment in future prospective studies to validate this metric.

5. Conclusions

This exploratory study provides preliminary evidence that the VTI-VeXUS index—a novel integration of arterial flow and venous congestion measurements—may identify patients at increased risk of mortality in septic shock. Although the sample size was limited and the analysis was univariate, the magnitude of the relative hazard of death at 30 days suggests this non-invasive metric warrants further investigation. Future prospective studies with larger cohorts and multivariable adjustment are required to validate these findings, establish optimal thresholds, and determine whether the VTI-VeXUS index can guide clinical decision-making in septic shock.

Author Contributions:

RP: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review and editing.

SP: Conceptualization, Data curation, Investigation, Methodology, Resources, Writing – review and editing.

HC: Data curation, Investigation, Visualization, Writing – review and editing.

RS: Data curation, Investigation, Visualization, Writing – review and editing.

NO: Investigation, Resources, Supervision, Writing – review and editing.

JEK: Formal analysis, Methodology, Software, Supervision, Writing – review and editing.

PR: Conceptualization, Methodology, Supervision, Writing – review and editing.

MW: Data curation, Writing – review and editing.

MS: Conceptualization, Formal analysis, Methodology, Supervision, Writing – review and editing.

KL: Formal analysis, Supervision, Validation, Writing – review and editing

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JB: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review and editing.

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Institutional Review Board Statement: This study was approved by the Western University Research Ethics Board (WREM Approval #120202).

Informed Consent Statement: We obtained consent from all patients or their substitute decision-makers using a deferred consent model. This enabled the inclusion of critically ill patients who were unable to provide consent at the time of enrollment.

Data are available upon request.

Conflicts of Interest: JEK is an employee at Flosonics Medical, a startup commercializing wearable Doppler ultrasound. None of the other authors have a conflict of interest to declare.

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METHODOLOGICAL ISSUES AND THESIS CONCLUSIONS

Our pilot work on the VTI-VeXUS ratio and systematic review of venous congestion in critically ill patients has demonstrated several important findings. First, venous congestion is likely associated with adverse outcomes, particularly acute kidney injury (AKI) and mortality in critically ill patients. Although venous congestion has been recognized for decades, only recently have clinicians begun using Doppler ultrasound to quantify it at the bedside. There are important research gaps that need to be addressed with high-quality, prospective, and eventually randomized trials. Existing studies have a significant risk of bias, particularly in the domain of

study confounding. Improved reporting of new VEXUS studies will help ensure they can be synthesized with the existing and growing evidence base.

Challenges with the Thresholds for Defining Venous Congestion

Venous congestion is inherently a continuous physiological variable, yet clinical assessments frequently categorize this variable to simplify decision-making for bedside clinicians.[19] While this approach is appealing, it has several potential limitations, most notably the relatively arbitrary thresholds incorporated into venous congestion scoring systems.

The most common ordinal ranking score for venous congestion is the VeXUS score. Despite its popularity, it may fail to accurately classify a patient's congestion in several situations. For example, it may overemphasize the degree of venous congestion in patients with baseline venous abnormalities such as pulmonary hypertension or severe tricuspid regurgitation, who often present with high VeXUS scores due to abnormalities in the hepatic and renal veins.[40] Alternatively, it may underestimate the prevalence of venous congestion in some patient populations, such as those with sepsis, where we hypothesize that lower thresholds of venous abnormalities may be associated with adverse outcomes. This is the subject of investigation in our Andromeda-VEXUS study.

Continuous indices such as the Portal Vein Pulsatility Index and the Renal Venous Stasis Index (RVSI) effectively capture the continuum of venous congestion.[12,41,42] However, this continuity is not universally applicable; hepatic vein assessments, for instance, currently lack widely adopted continuous measurements, although emerging approaches show promise.[43]

From a statistical standpoint, treating venous congestion as a continuous variable preserves power and maximizes the use of available data, especially in multivariable regression models

where continuous data are counted as one degree of freedom. This is useful when approximating sample size requirements using a 10:1 rule of events to degrees of freedom in multivariable regression. However, the precision of this approach is an area of ongoing discussion.[44] Categorization, while clinically intuitive, risks misclassification, potentially weakening associations and underestimating true effects. In general, continuous measures allow for more precise adjustment in multivariable models, enable the detection of dose-response relationships, and support the identification of clinically relevant thresholds, which can be determined using methods such as restricted cubic splines.[45]

For the meta-analysis performed as part of this thesis, the ordinal nature of the VEXUS score created difficulties in choosing the appropriate threshold for determining congestion. Most studies reported a cutoff of VEXUS 2 or 3 to define congestion; however, some studies analyzed VEXUS scores of 1, 2, or 3 as representing congestion. Based on clinical and early VEXUS work, including VEXUS 1 as congested is inappropriate, as these patients do not have an increased risk of developing AKI.[19] Nonetheless, methodologically, the ordinal nature and desire for categorization create challenges for VEXUS researchers.

Overall, the continuous nature of venous congestion creates challenges for researchers and clinicians attempting to select appropriate scoring systems. Future research studies should record congestion markers as continuous variables, allowing for individualized thresholds based on specific pathophysiologic contexts. For example, in our ongoing prospective Andromeda-VEXUS study, we record IVC, hepatic vein, portal vein, and renal vein measurements as continuous values, whose optimal thresholds for predicting congestion will be re-evaluated for patients with septic shock.[16]

Limitations in Measuring Association: HR versus OR

Another methodological challenge in studying venous congestion that arose during the meta-analysis for our systematic review is the difference between hazard ratio (HR) and odds ratio (OR), both of which have been used variably to measure the association between venous congestion and outcomes of interest. Hazard ratios consider not just whether an event occurred but also the timing of events, thus capturing early divergence in patient outcomes such as death or dialysis initiation, which is essential for critically ill populations.[46] In contrast, odds ratios do not account for time-to-event dynamics and may miss survival curves that diverge early but converge at later time points. For many patients, in addition to the outcome of their ICU admission (e.g., death), their course within the ICU is important (e.g., requiring organ support or RRT), as it is burdensome and potentially causes distress. Thus, factoring in the timing of organ support in addition to outcomes at the end of a follow-up period is important.

Our previous pilot study of venous congestion in septic shock demonstrated that early physiological derangements might be missed when examining ORs alone.[12] For Andromeda-VEXUS, our multicenter prospective study of venous congestion in septic shock, we are preferentially choosing time-to-event analyses to adequately capture the dynamic nature of venous congestion and the impact of organ support on both the quantity and quality of life for ICU patients.

Although it may be tempting to increase statistical power by pooling these measures, doing so risks introducing bias, as hazard ratios (HRs) and odds ratios (ORs) lie on different scales (logistic regression vs. survival analysis) and exhibit different properties. Although some methods exist to approximate a common effect measure, such as converting ORs to approximate risk ratios[47], these approaches rely on assumptions about baseline risk and event rates that may

not hold across diverse populations. For our meta-analysis, we elected to pool only the ORs presented in the primary studies.

Confounding and Causal Pathways in Venous Congestion

Venous congestion research faces inherent difficulties in distinguishing prognostic associations from causative relationships due to potential confounding and unreported co-interventions. Right-sided venous congestion frequently occurs alongside clinical signs of fluid overload, such as peripheral edema or pulmonary edema (which is left-sided congestion) on imaging, which could independently drive interventions (e.g., diuretics or inotropes) that modify outcomes. The importance of reporting co-interventions is highlighted in the QUIPS risk of bias tool, and, as seen in our systematic review, these were inadequately reported for most of the included studies[48].

There are several potential consequences of unmeasured confounders and unreported co-interventions in this context. First, co-interventions, such as diuretics or inotropes, may partially mitigate the association between venous congestion and adverse outcomes, as the condition is recognized and treated. This could help explain why early differences in outcomes may not persist at later time points. Alternatively, if venous congestion is not causally linked to adverse outcomes but instead serves as a marker of illness severity, the omission of key variables, particularly measures of cardiac function, may exaggerate the clinical relevance of congestion as a therapeutic target.

These issues have important implications for future research. Studies should explicitly report relevant co-interventions, including diuretic use, inotropic support, and other hemodynamic therapies. Additionally, future work should routinely assess cardiac function, especially right

ventricular (RV) function, and consider the role of congestion in the context of RV failure. A central question remains: Does RV failure alone account for the adverse outcomes observed in patients with venous congestion, or does congestion contribute independently as a direct mechanism of organ injury? This could be addressed by considering RV dysfunction as a covariate in observational studies when examining the relationship between venous congestion and adverse outcomes. However, this requires nuance, as the role of RV dysfunction in the causal framework of venous congestion remains uncertain. RV dysfunction may act as a confounder, reflecting overall cardiovascular compromise, predisposing to congestion and downstream organ injury. Alternatively, it could serve as an effect modifier, amplifying the impact of congestion in certain clinical contexts. There is also the possibility that RV dysfunction lies directly within the causal pathway, mediating the progression from RV dysfunction to venous congestion and subsequent organ dysfunction. Disentangling these relationships is critical to clarify whether venous congestion itself is a modifiable target for intervention or simply a surrogate marker of more complex cardiac pathology.

Challenges in Choosing a Threshold for the VTI-VeXUS Threshold

The integration of venous and arterial hemodynamics through metrics such as the VTI-VeXUS ratio shows an association between higher scores and worse outcomes. However, choosing the optimal threshold of VTI-VeXUS that predicts mortality was not straightforward. Initially, we used a receiver operating characteristic (ROC) analysis to determine the VTI-VeXUS ratio most predictive of mortality. The value obtained, however, was at a threshold that only approximately 20% of the patients met. Given that we intend the VTI-VeXUS ratio to be useful clinically, the asymmetry between groups meant it would not be applicable to most patients, so we opted to use the median VTI-VeXUS score instead. This was an acceptable approach as it remained

significantly associated with an increased hazard for mortality. The disadvantage of this approach is that, while improving applicability to the overall cohort, it may underestimate the risk in the most severely affected patients.

An alternative approach would have been to study the VTI-VeXUS as a continuous variable, for many of the reasons discussed in previous sections. We opted against this because we wished to simplify this already complicated concept to help clinicians at the bedside quickly screen for patients who might be at increased risk of adverse outcomes and who would warrant further investigation. Thus, thresholding these patients into high and low scores became relevant.

The dichotomization of VTI-VeXUS into "high" and "low" is another example of the inherent complexity and limitations of turning continuous variables into categorical ones. On one hand, the strongest statistical association is desired to be confident in the threshold chosen; however, this might occur at a value that is not actually useful in clinical practice.

Final Knowledge Gaps and Future Research Directions

Venous congestion is increasingly considered an important factor in septic shock, yet key gaps remain concerning its clinical application and measurement methodologies. Specifically, the precise thresholds of venous congestion associated with adverse outcomes remain poorly defined. Future high-quality observational studies, such as the Andromeda-VEXUS study[16], are needed to clarify these thresholds and examine whether simplified metrics (e.g., portal vein pulsatility) could match the diagnostic performance of comprehensive scoring systems. Additionally, the clinical implications of integrating venous congestion management with broader hemodynamic strategies need clarification. For example, does a patient with venous congestion early in septic shock benefit from, or is harmed by, the administration of diuretics and

other therapies targeted towards congestion? This is the research question for a pilot randomized controlled trial being conducted by our team led by Dr. Basmaji. Ultimately, well-designed observational and interventional studies are necessary to fully understand how, and when, to integrate venous congestion assessments into clinical practice.

CONCLUSIONS

Venous congestion appears to be associated with adverse outcomes, but its role in the causal pathway remains uncertain. The current evidence indicates that venous congestion may be associated with adverse outcomes, particularly acute kidney injury, in critically ill patients. However, whether venous congestion directly contributes to organ injury or is merely a marker of underlying disease severity remains unresolved. Moreover, limitations in the reporting of co-interventions and confounders in existing studies obscure causal inference. Future research must prioritize methodological rigor, including robust adjustment for right ventricular function and precise measurement of both congestion and therapeutic interventions, to determine whether venous congestion is a modifiable therapeutic target or simply an epiphenomenon of severe circulatory failure.

Integrating forward flow and venous congestion offers a more complete understanding of hemodynamics than either in isolation. Traditional hemodynamic assessment in septic shock has focused predominantly on forward flow, neglecting the influence of venous pressures and congestion. The findings of this thesis suggest that considering both arterial output and venous congestion provides a more comprehensive evaluation of circulatory status. The VTI-VeXUS ratio is one potential integrative approach. Moving forward, strategies that unify arterial and

venous assessments should guide both diagnostic frameworks and therapeutic decision-making, recognizing that shock states cannot be fully understood through isolated variables alone.

Future research demands better measurement, adjustment for confounders, and improved reporting standards. A critical barrier to progress in this field is the quality and consistency of primary literature. Most existing studies are limited by small sample sizes, observational designs, and insufficient adjustment for confounding variables such as cardiac function and co-interventions. Furthermore, dichotomizing inherently continuous variables like venous congestion risks oversimplification and loss of important prognostic information. Future studies should embrace continuous data capture and analytic strategies that allow for a nuanced understanding of dose-response relationships and identification of clinically meaningful thresholds. High-quality, multicenter prospective studies with standardized protocols and transparent reporting of therapies administered will be essential to clarify the prognostic versus causal role of venous congestion and evaluate whether targeted interventions can modify its trajectory and improve patient outcomes.

Final Reflections

Throughout this thesis, I have reflected on an old quote from Lord Kelvin*: "When you can measure what you are speaking about, and express it in numbers, you know something about it; when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of science.*" Venous congestion is not a new entity; however, portable Doppler ultrasound is the technology that allows clinicians to *"measure what we are speaking about, express it in numbers, ... and advance to the stage of scienc*e." While future qualitative and mixed methods research will be essential to understand the barriers and facilitators to implementing venous

congestion assessment at the bedside, we now have shared language to quantify congestion and design high quality prospective studies.

While much is uncertain about venous congestion, this much is clear: we are only in the infancy of understanding the complex interplay between venous and arterial physiology. Does an association between congestion and adverse outcomes exist? Almost certainly. Will integrating venous and arterial physiology into a comprehensive conceptual model help us better understand our patients' shock states? We believe so. Beyond this remains the realm of exciting discovery where scientists can aspire to understand a unified theory of congestive physiology.

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