

Vascular stiffness and sepsis mortality: A promising signal in search of clinical relevance

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Sepsis is a major contributor to all-cause mortality worldwide and is a leading cause of in-hospital deaths in Southeast Asia.¹ The emergence of SARS-CoV-2 significantly disrupted a steady trend of improving sepsis survival over the last 30 years; fortunately, that trend appears to have resumed in 2023.

Improvement in sepsis mortality outcomes has been attributed to early sepsis recognition and to protocolising a prompt response to sepsis, including moderate fluid resuscitation and early initiation of context-appropriate antibiotics. While outcome improvements are commendable, 30-day mortality due to septic shock still averages 34.7% (95% confidence interval [CI] 32.6–36.9%) and sepsis without shock averages 24.4% (95% CI 21.5–27.2%) with modest regional variation.² The potential utility of mortality prognostication seems clear. Accurate mortality prognostication could improve goals-of-care conversations, triage considerations, resource stewardship in the intensive care unit (ICU), and clinical trial enrolment. However, unlike the established benefits of early sepsis recognition and timely intervention, the extent to which improved mortality prognostication translates into better individual patient outcomes remains unclear. At present, its utility may be greater for population-level benchmarking rather than for bedside management.³

As the understanding of sepsis pathophysiology evolved from the 1980s into the 1990s, so did sepsis mortality prognostication. Starting with simple physiological scoring tools including Acute Physiology and Chronic Health Evaluation (APACHE), APACHE II, Simplified Acute Physiology Score (SAPS), SAPS II, and SAPS III, prognostic models subsequently progressed towards complex organ dysfunction assessment using Sequential Organ Failure Assessment (SOFA). These instruments were initially validated for use during the first 24 hours in the ICU (APACHE and SAPS families) or for serial use in the ICU (SOFA), but subsequent evaluation has supported their use outside the ICU in the emergency department and in general wards. The APACHE and SAPS tools demonstrate area under the receiver

operating characteristic (AUROC) values in the 0.75–0.90 range, whereas SOFA's AUROC value range is 0.80–0.92. AUROC values in these ranges reflect good-to-excellent discrimination for predicting mortality. Multiple approaches intending to incrementally improve mortality prognostication are underway: biomarker and physiological marker combinations (e.g. adjusted quick SOFA using lactate and procalcitonin), enhanced clinical scoring systems (e.g. National Early Warning Score and Modified Early Warning Score, APACHE IV), machine learning models, and transcriptomics.⁴

Estimated pulse wave velocity (ePWV) has recently entered the sepsis mortality prognostication landscape. Unlike carotid-femoral pulse wave velocity (cfPWV), which is measured using specialised equipment to directly quantify pressure wave speed along the aorta, a patient's ePWV value can be generated via several methods of varying accuracy. The method utilised by Ding et al. calculates ePWV (hereafter labelled "derived ePWV") using a regression equation that was empirically derived and validated in a pan-European reference population, which excluded subjects with diabetes mellitus, treated hypertension, treated dyslipidaemia or known cardiovascular disease. The calculation requires only mean blood pressure and patient age.⁵ cfPWV is the gold standard for measuring aortic stiffness and predicts cardiovascular events independently of traditional risk factors (age, sex, systolic blood pressure, body mass index, smoking, cholesterol).⁶ Derived ePWV's correlation with cfPWV is modest ($r=0.67$) and decreases further in patients with diabetes mellitus and those with chronic kidney disease.⁷ Derived ePWV independently predicts all-cause mortality, but not cardiovascular events.⁸ Derived ePWV is more accessible than cfPWV and other direct measures of pulse wave velocity. The rationale for investigating pulse wave metrics is grounded in observations of sepsis-related endothelial injury and vascular dysregulation.^{9,10} Both cfPWV and derived ePWV have been explored as tools for predicting sepsis-related mortality risk with mixed results.¹¹ In Ding et al., derived ePWV shows a signifi-

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cant linear positive association with 28-day mortality in septic ICU patients with some caveats.¹² Ding et al. present what appears to be a statistically strong case for derived ePWV to incrementally improve prediction, but the issue of clinical relevance remains. In their study, derived ePWV used alone had a poor AUROC value of 0.567. The 2 prediction models they compared head-to-head are the “combined LASSO model” and the “adjusted model”. Importantly, both the “adjusted model” and the “combined LASSO model” already include derived ePWV. The modest increase in AUROC from 0.815 to 0.823 likely reflects improved statistical discrimination from LASSO-based variable selection rather than a clearly demonstrated incremental contribution from ePWV itself. Notably, they do not provide head-to-head performance results of their 2 models with existing sepsis prognostic scores (SOFA, APACHE, etc.) or assess their 2 models without including ePWV. As such, the hypothesis that derived ePWV is useful as a sepsis mortality prognosticator alone or that it makes a clinically significant or practical contribution to sepsis mortality prognostication models or existing scoring systems is not established.¹²

The authors are to be commended for leveraging the Medical Information Mart for Intensive Care (MIMIC-IV) as a large real-world resource for studying septic ICU patients, strengthening evidence for an association—rather than a correlation—between ePWV and sepsis mortality that prior small cohort studies have demonstrated less convincingly, and demonstrating that ePWV retains statistical significance after extensive adjustment. However, because ePWV is mathematically derived from age and mean blood pressure, performs poorly as a standalone predictor (AUC 0.567), and was not directly compared against existing prognostic tools with and without its inclusion, its value remains uncertain.

With respect to the generalisability of this work to Asia, readers should be aware of the limitations of the tool and materials used to test the prognostication models by Ding et al.: derived ePWV and MIMIC-IV. Derived ePWV was empirically generated from a predominately non-Asian population, which excluded those with diabetes mellitus, treated hypertension, cardiovascular disease or treated dyslipidaemia. The MIMIC-IV database is derived from a single medical centre in the US where ICU practices, mortality rates, disease epidemiology, and end-of-life cultural perspectives may differ substantially from those encountered in Asia. Notably, Asians represent <5% of MIMIC-IV’s cohort. Although these limitations are not disqualifying, contextually relevant validation—with local ICU practices, appropriate ethnic representation, and prevalent regional comorbidities—would strengthen confidence in the findings.

In this context, the work by Ding et al. is best viewed as an exploratory effort that strengthens evidence for an association between derived ePWV and sepsis mortality while leaving its clinical value unresolved. Future studies should demonstrate not only improved statistical discrimination and generalisability but also meaningful impacts on clinical decision-making and patient outcomes.

Ethics statement

Not applicable, as no study participants were involved.

Declaration

The author declares that he has no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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