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SYSTEMATIC REVIEW & META-ANALYSIS

Monocyte Distribution Width as a Prognostic Biomarker of Mortality in Adult Patients with Sepsis or Severe Infection: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Monocyte distribution width (MDW) is reported automatically with a routine complete blood count. Its diagnostic accuracy for sepsis has been meta-analysed repeatedly, but no synthesis has asked whether it predicts death once sepsis is present.

Objective: To determine whether admission MDW predicts all-cause mortality in hospitalised adults with sepsis or severe infection.

Methods: Three databases were searched for cohorts of hospitalised adults with sepsis or severe infection reporting admission MDW against all-cause mortality. The standardised mean difference (Hedges' g) was derived through three tiers (group means, mortality-AUC conversion, and 2 × 2 tables) and pooled with a DerSimonian–Laird random-effects model; risk of bias used the QUIPS tool.

Results: Twelve cohorts from eight countries were included (2,289 patients; 475 non-survivors). MDW was higher in non-survivors (pooled Hedges' g = 0.60, 95% CI 0.39 to 0.80; $p < 0.001$; $I^2 = 50.8\%$), robust across all twelve leave-one-out models (0.56 to 0.64). Elevated MDW carried roughly five-fold higher odds of death (OR 4.68; k = 9), but discrimination was modest (pooled AUC 0.676; k = 8). The pooled OR fell from a crude 3.99 to 2.68 after severity adjustment. No small-study effects were detected (Egger p = 0.846); certainty was low.

Conclusion: Admission MDW was consistently higher in adults with sepsis or severe infection who died. The association was moderate, not confined to COVID-19 and survived severity adjustment, but discrimination was insufficient for individual prognostication and no threshold is recommended; MDW is best regarded as an adjunct to established severity scores.

1. Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, with septic shock representing the subset in which circulatory, cellular and metabolic derangements are profound enough to increase mortality substantially.[1] The burden remains formidable and is concentrated in Asia. An analysis of the Global Burden of Disease Study showed that sepsis incidence and sepsis-related mortality in China remained among the highest absolute burdens worldwide over three decades,[2] and a national registry study of emergency department attendances confirmed that sepsis continues to account for a substantial share of emergency admissions and of subsequent in-hospital death.[3] Because delays in recognition translate directly into delays in antimicrobial therapy, and because such delays are associated with worse outcomes, any test that shortens the interval between presentation and recognition is of direct clinical interest.[4]

Risk stratification in sepsis has traditionally relied on composite clinical scores and on circulating inflammatory biomarkers. C-reactive protein rises in both infectious and non-infectious inflammation and therefore lacks specificity, whereas procalcitonin, although more specific for bacterial infection, performs inconsistently in early disease and in non-bacterial sepsis.[5,6] Both markers require a dedicated assay, incur additional cost and add turnaround time. In resource-constrained health systems, including district hospitals across Indonesia, these constraints materially limit how often such tests are ordered at the point where a triage decision is actually made.

Monocyte distribution width (MDW) emerged from this gap. MDW is the standard deviation of the volumes of circulating monocytes and therefore quantifies monocyte anisocytosis rather than monocyte number. The informative quantity is the heterogeneity of monocyte volume rather than the mean volume, and the reason is worth stating explicitly. During early innate immune activation, recognition of pathogen-associated and damage-associated molecular patterns triggers cytoskeletal reorganisation, vacuolisation, filopodia formation and changes in surface protein expression. Individual monocytes enter this process asynchronously and respond to differing degrees, so at any given moment the circulating pool contains cells at every stage from quiescent to fully activated. The mean volume of such a mixed population may shift only marginally, because activated and unactivated cells offset one another, whereas its dispersion rises immediately and steeply. Monocyte anisocytosis therefore detects the onset of a heterogeneous activation response earlier than any measure of central tendency could. Critically, MDW is computed automatically by volume, conductivity and scatter technology as part of a routine complete blood count, requires no additional blood draw and no additional reagent, and is reported within the turnaround time of the full blood count itself.[7,8]

The diagnostic performance of MDW has been examined intensively. Multicentre cohorts established that MDW discriminated sepsis from non-infectious illness in emergency department patients and added information beyond conventional criteria,[9-11] and further cohorts extended this to intensive care, to patients living with HIV, to post-operative urosepsis and to blood-culture triage.[12-15] That evidence base has since been synthesised repeatedly: at least five systematic reviews with meta-analysis have pooled the diagnostic accuracy of MDW for sepsis,[5,16-20] and further syntheses have addressed its role in COVID-19.[21-23] Whether or not the underlying science is settled, the volume of existing

synthesis on the diagnostic question is such that a further diagnostic review would add little.

A different and clinically distinct question has not been answered. Diagnostic accuracy addresses whether MDW identifies the patient who has sepsis. Prognostic value addresses whether, among patients who already have sepsis, MDW identifies the patient who will die. These are separate constructs with separate reference standards, and a biomarker may perform well on one and poorly on the other. Individual cohorts have reported that MDW predicted short-term mortality and was the only biomarker significantly higher in non-survivors,[12,24,25] that MDW kinetics rather than a single admission value carried the prognostic signal,[26,27] and that MDW did not discriminate mortality at all.[28] These conflicting findings have never been pooled, and the extent to which any prognostic association is independent of illness severity has never been quantified across studies.

A conceptual point should be made at the outset, because it determines how the present evidence must be appraised. MDW is a measurement rather than an intervention. Patients cannot be randomly allocated to a high or a low monocyte distribution width, and consequently no randomised controlled trial of MDW as a prognostic factor exists or could exist. The highest attainable level of evidence for this question is the prognostic cohort study, and instruments designed for randomised trials do not apply to it. This constrains both the design of the present review and the certainty that any synthesis of this literature can achieve.

The novelty of this study lies in being the first systematic review and meta-analysis to address the prognostic rather than the diagnostic value of monocyte distribution width in adults with sepsis or severe infection, in harmonising twelve cohorts that reported their results on three different statistical scales onto a single effect measure using pre-specified and validated conversions, and in quantifying for the first time how much of the crude association between monocyte distribution width and death survives adjustment for illness severity. The aim of this study was to determine whether monocyte distribution width measured at or near hospital admission was higher in adults with sepsis or severe infection who subsequently died than in those who survived, to estimate the magnitude of that difference and the associated odds of death, to assess how well monocyte distribution width discriminated survivors from non-survivors, and to establish whether any observed association was explained by the severity of the underlying illness.

2. Methods

Design and reporting

This study was designed as a systematic review with random-effects meta-analysis of observational prognostic cohort studies and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[29] The review question was framed in prognostic terms. The population comprised adults hospitalised with sepsis or severe infection, the prognostic factor was monocyte distribution width measured at or near admission, and the outcome was all-cause mortality as reported by each study. No amendment was made to the analysis plan after the data were inspected.

Search strategy

Three databases were searched: PubMed, Europe PMC and CrossRef. No date limit was applied, which was appropriate because monocyte distribution width was first described as a sepsis biomarker in 2017 and no relevant literature predates that point. The Boolean search string applied in PubMed was:

("monocyte distribution width"[All Fields] OR "monocyte anisocytosis"[All Fields] OR MDW[tiab]) AND (sepsis OR septic OR "suspected infection" OR "severe infection") AND (mortality OR death OR survivor\ *OR non-survivor*\ OR fatal OR prognos* OR "in-hospital" OR "28-day" OR "30-day" OR outcome)

Equivalent free-text queries were executed against the Europe PMC and CrossRef application programming interfaces in order to capture journals that are indexed outside MEDLINE. This decision proved material: two included cohorts, one published in the *Malaysian Journal of Anaesthesiology* and one in the *Indian Journal of Hematology and Blood Transfusion*, were recovered only through those supplementary sweeps. The reference lists of five previous systematic reviews of monocyte distribution width were checked manually for additional eligible reports.[16,17,19-21] Every record returned by every executed query was retrieved and screened; no relevance cap and no sampling of the result set were applied.

Eligibility criteria

Studies were eligible if they satisfied all of the following: they were original research articles; they used a prospective or retrospective cohort design, or reported a secondary analysis of a prospective cohort; they enrolled adults aged 18 years or older who were hospitalised with sepsis, septic shock, suspected infection or severe infection, including infection caused by SARS-CoV-2; monocyte distribution width was measured on a volume, conductivity and scatter haematology analyser at or near admission; all-cause mortality was reported as an outcome, whether in-hospital, intensive care unit, 28-day or 30-day mortality; and sufficient data were reported to derive a standardised mean difference through one of the three pre-specified routes described in *Effect measures and derivation tiers*.

Studies were excluded if they were narrative reviews, systematic reviews, meta-analyses, editorials, commentaries, letters without original data, case reports, conference abstracts or preprints; if they were conducted in animals or in vitro; if the population was exclusively paediatric or neonatal, a body of evidence that is developing separately and behaves differently;[30,31] if the population was non-septic, for example cohorts limited to chronic obstructive pulmonary disease exacerbation, burns, elective pancreatic surgery or diverticulitis; if only diagnostic accuracy was reported with no mortality outcome; or if the report duplicated a cohort already included. Where two reports appeared to describe the same patients, the report providing the more complete mortality data was retained and the other was excluded as a duplicate cohort.

Study selection and data extraction

Records were de-duplicated across the three databases and screened on title and abstract, after which full texts were sought for all potentially eligible reports. Screening and extraction were performed by one reviewer. A second verification pass was then conducted, and its scope is specified here so that readers may judge its adequacy: every one of the 38 reports sought for retrieval was re-read in full against the eligibility criteria, and every numerical value entering the analysis was independently re-extracted from the source full text and compared against the first extraction, with any discrepancy resolved by returning to the source. The verification pass did not, however, involve a second independent screen of the 704 titles and abstracts. This process therefore does not constitute dual independent review, and the possibility that an eligible study was missed at the title-and-abstract stage cannot be excluded. This is a material limitation and is discussed in *Strengths and limitations*.

Six reports were sought but could not be retrieved, because their full texts lay behind subscription paywalls or existed

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only as conference abstracts and the accessible portion contained insufficient data to derive any effect estimate through any of the three routes described below. Their published abstracts were nonetheless read, and the direction of the association each reported is stated in *Study selection* so that readers may judge the likely direction of any resulting bias.

For each included study the following were extracted: first author, year, country, setting and level of care, study design, sepsis or infection definition and reference standard, total enrolled, numbers of non-survivors and survivors with vital-status data, the definition and timing of the mortality outcome, the timing of monocyte distribution width sampling, the analyser used, the study-specific cut-off, and every reported statistic relating monocyte distribution width to mortality. No value was imputed, assumed or carried forward from a secondary source; every number entered into the analysis was traced to the source full text.

Effect measures and derivation tiers

The primary effect measure was the standardised mean difference expressed as Hedges' g, with the small-sample correction applied and with positive values denoting higher monocyte distribution width in non-survivors. A standardised measure was chosen in preference to a raw mean difference because monocyte distribution width was reported in different units across studies and was measured on different analyser configurations, and because a standardised measure is invariant to any linear rescaling of the underlying variable.

Only three of the eligible cohorts reported monocyte distribution width as a mean and standard deviation separately for non-survivors and survivors. Restricting the synthesis to those three would have produced an underpowered and uninformative analysis. Three derivation tiers were therefore pre-specified. Tier A used directly reported means and standard deviations and applied the standard Hedges' g formula, in which the pooled standard deviation is

$$s_p = \sqrt{[\,((n_1 - 1)s_1^2 + (n_2 - 1)s_2^2) / (n_1 + n_2 - 2)\,]}$$

$$g = J \cdot (M_1 - M_2) / s_p\,,\ J = 1 - 3 / [\,4(n_1 + n_2 - 2) - 1\,]$$

Tier B applied to studies reporting a mortality area under the receiver operating characteristic curve together with group sizes, converting the area under the curve to a standardised mean difference by the relation[32]

$$g = \sqrt{2} \times \Phi^{-1}(AUC)$$

where Φ^{-1} denotes the inverse standard normal cumulative distribution function. Tier C applied to studies from which a 2 × 2 table of death by monocyte distribution width above or below the study-specific cut-off could be reconstructed, converting the resulting log odds ratio to a standardised mean difference by[33]

$$g = \ln(OR) / 1.8138,\ var(g) = var(\ln OR) / 1.8138^2$$

A conservative variance rule was applied to Tier B. The standard error of the area under the curve was taken as the larger of the standard error implied by the published confidence interval and the Hanley–McNeil standard error computed from the numbers of deaths and survivors.[34] Several reports published confidence intervals that were implausibly narrow given the small number of deaths observed, and this rule prevented such studies from dominating the pooled estimate.

The assumptions underlying these conversions require explicit statement. The area-under-the-curve transformation assumes that monocyte distribution width is normally distributed within each vital-status group with approximately equal variance; the odds-ratio transformation assumes an underlying logistic distribution of the same latent quantity. Neither assumption can be verified from published aggregate data, and there is circumstantial reason to doubt strict normality: monocyte distribution width is itself a dispersion statistic, is bounded below, and is plausibly right-skewed in septic populations in which a subset of patients exhibits extreme monocyte activation. Several included reports present medians with interquartile ranges rather than means, which suggests that their own authors regarded the distribution as non-normal. Right skew in both groups tends to attenuate a standardised mean difference derived from an area under the curve towards the null, so the resulting bias would be expected to be conservative rather than inflationary, but this expectation cannot be confirmed without individual patient data. The derivation route was carried forward as a pre-specified moderator so that any systematic difference between tiers could be detected.

Two distinct validation steps should not be conflated. The first is arithmetic: reconstructed 2 × 2 tables were checked against the odds ratios published by the source studies, and two tables read directly from full texts reproduced their published odds ratios exactly, while a table reconstructed from published sensitivity, specificity and group sizes reproduced a published univariable odds ratio exactly. These checks confirm that the reconstruction rule was applied correctly. They do not, and cannot, validate the subsequent conversion of an odds ratio or an area under the curve into a standardised mean difference, which depends on the distributional assumptions set out above and could only be validated against individual patient data. The present review therefore offers arithmetic validation of the reconstruction and statistical testing of the derivation route as a moderator; it does not offer distributional validation of the transformations themselves.

Risk of bias assessment

The instrument used was the Quality In Prognosis Studies (QUIPS) tool rather than the Cochrane Risk of Bias 2.0 instrument, and the reason is placed first because some readers will arrive expecting the latter. Risk of Bias 2.0 is defined only for randomised controlled trials. As set out in the introduction, monocyte distribution width is a measurement rather than an intervention, no randomised evidence exists or can exist for this question, and no eligible study was randomised; applying an instrument built around allocation concealment, deviation from intended interventions and randomisation-based blinding would therefore have been methodologically incoherent and would have produced uninterpretable ratings. QUIPS is the instrument recommended for prognostic factor reviews. The substitution is reported as a deliberate and documented deviation rather than an oversight, and it is reiterated in *Strengths and limitations*.

Risk of bias was accordingly assessed across the six QUIPS domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Each domain was rated as low, moderate or high risk, and an overall rating was assigned. The two cohorts recovered from journals not indexed in MEDLINE were assessed with exactly the same instrument, by the same reviewer and against the same criteria as the remaining ten, and both appeared in peer-reviewed journals.

Statistical analysis

Effect estimates were pooled with a random-effects model using the DerSimonian–Laird estimator of the between-study variance. Heterogeneity was quantified with τ^2, τ, the I^2 statistic, H^2 and Cochran Q, and a 95% prediction interval was computed to express the range of effects expected in a future comparable cohort. Restricted maximum likelihood, Paule–

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Mandel and Hartung–Knapp–Sidik–Jonkman models, together with a fixed-effect model, were fitted as robustness checks.

Six subgroup analyses were conducted using mixed-effects meta-regression with a test for subgroup differences, examining aetiology of the septic insult, level of care at sampling, study design, overall risk of bias and route of effect-size derivation. Seven meta-regressions were fitted on study-level moderators: cohort mortality rate, publication year, log total sample size, aetiology, level of care, design and derivation route. Sensitivity analyses comprised leave-one-out analysis, influence diagnostics including studentised residuals, DFFITS, Cook's distance, hat values and a Baujat plot, cumulative meta-analysis ordered by publication year, and fourteen restricted or alternative models.

Two secondary analyses were pre-specified. First, a pooled odds ratio for mortality comparing elevated with non-elevated monocyte distribution width was computed from studies contributing a 2 × 2 table. Second, the reported mortality areas under the curve were pooled on the logit scale to summarise discrimination. A third, explanatory analysis compared crude and severity-adjusted estimates within the subset of studies reporting both.

Because twelve studies were included, assessment of small-study effects was mandatory. Funnel plots were inspected visually, Egger regression with the standard error as predictor and the Begg rank correlation test were performed, the Duval–Tweedie trim-and-fill procedure was applied, and the Rosenthal fail-safe N was computed. Each of these procedures has recognised limitations at this number of studies and they are interpreted accordingly. The Begg rank correlation test has low power with twelve studies, so a non-significant result is uninformative rather than evidence that bias is absent. The Rosenthal fail-safe N assumes that any unpublished studies would have a mean effect of exactly zero, which is implausible, and the statistic is known to be liberal; it is reported for completeness rather than as evidence. Trim-and-fill imputes hypothetical studies and its output is a thought experiment rather than a corrected estimate.

All analyses were performed in R version 4.4 using the *metafor* package. Certainty of the evidence was rated using the GRADE framework as adapted for prognostic factor studies. Statistical significance was interpreted at a two-sided alpha of 0.05, with emphasis placed on the width and position of confidence intervals rather than on dichotomous significance testing.

3. Results

Study selection

The three database searches returned 847 records in total: 86 from PubMed, 615 from Europe PMC and 146 from CrossRef. After 143 duplicate records indexed in more than one database were removed, 704 records were screened on title and abstract. Of these, 666 were excluded: 402 were not clinical studies of monocyte distribution width, 158 evaluated monocyte distribution width for diagnosis only with no mortality or other prognostic outcome, 71 were reviews, editorials, letters, case reports or conference abstracts, and 35 studied paediatric, neonatal, non-human or non-infectious populations. Full texts were sought for 38 reports, of which 6 could not be retrieved. Of the 32 reports assessed for eligibility, 20 were excluded: 11 reported no monocyte distribution width to mortality contrast and no convertible effect estimate, 4 studied non-septic populations, 3 were systematic reviews used only for reference checking, and 2 studied neonatal or paediatric populations. Twelve studies were included in both the qualitative and the quantitative synthesis. The complete selection pathway, with the reason and count for every exclusion at every stage, is set out in Figure 1.

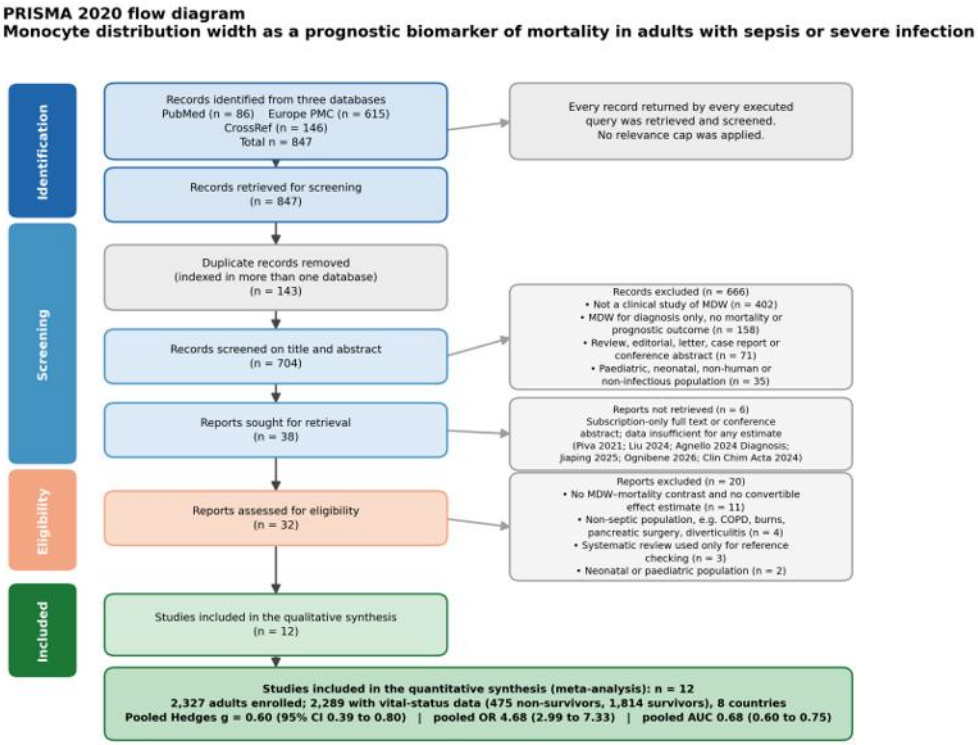

Figure 1. PRISMA 2020 flow diagram for the identification, screening and inclusion of studies. Records were retrieved from PubMed, Europe PMC and CrossRef, supplemented by reference checking of five systematic reviews. Every record returned by every executed query was screened and no relevance cap was applied.

The six reports that could not be retrieved warrant specific comment, because their absence is a potential source of bias that the tests for small-study effects cannot detect. Those tests examine asymmetry among studies that were included; they are silent about studies that were never available. From the published abstracts of the six unretrieved reports, five described monocyte distribution width as higher in patients with worse outcomes or reported a significant association with mortality, and one reported that admission monocyte distribution width did not predict death whereas its trajectory over the first five days did. The direction of effect in the unretrieved literature therefore appears broadly concordant with the pooled estimate, which argues against systematic exclusion of null results, although the sixth report is a reminder that the timing of measurement may matter more than the absolute value. At least two of the unretrieved cohorts were large intensive care series and would have contributed substantial weight had their full texts been obtainable.

Characteristics of the included studies

The twelve included cohorts[35-46] enrolled 2,327 adults, of whom 2,289 had vital-status data available and contributed to the analysis: 475 non-survivors and 1,814 survivors. Studies originated from eight countries, namely Italy (three cohorts), India (two), Serbia (two), and one each from Malaysia, Thailand, the United States, Taiwan and Greece. Eight studies were prospective and four retrospective. Eight cohorts were recruited in intensive care and four in emergency departments, general wards or mixed inpatient settings. Seven cohorts comprised patients with COVID-19 and five comprised patients with bacterial or mixed sepsis. Cohort mortality varied more than nine-fold, from 6.9% in the Indian COVID-19 cohort spanning the full severity spectrum[38] to 66.2% in the Serbian intensive care cohort of COVID-19 sepsis.[40] Study-specific cut-offs used in the primary analysis ranged from 21.86 to 36 units; across the wider set of studies contributing to the secondary odds-ratio analysis the range extended from 20 to 36 units. Three studies contributed a Tier A effect size derived from directly reported means, six contributed a Tier B effect size derived from a reported mortality area under the curve, and three contributed a Tier C effect size derived from a 2 × 2 table. No randomised trial was identified, and none exists for this question. The full characteristics of every cohort, together with its individual effect estimate, are detailed in Table 1.

Table 1. Characteristics of the twelve included prognostic cohort studies, with the individual effect estimate contributed by each. AUC denotes area under the receiver operating characteristic curve; QUIPS denotes the overall Quality In Prognosis Studies rating; MDW cut-offs are given in the units reported by each study.

Study (year)	Country	Population	Setting	Design	Deaths / surv.	Mort. (%)	Mortality outcome	Cut-off (U)	Effect source	QUIPS	Hedges' g (95% CI)
Riva 2021[35]	Italy	COVID-19	Infectious-disease unit + ICU	Prospective	16 / 71	18.4	Fatal outcome in hospital	26.4	Mortality AUC	Moderate	1.00 (0.34 to 1.66)
Soo 2022[36]	Malaysia	Critically ill incl. sepsis (66%)	ICU	Prospective	23 / 77	23.0	30-day mortality	25.97	Mortality AUC	Moderate	0.91 (0.36 to 1.46)
Lorubbio 2022[37]	Italy	COVID-19 (severe)	Pneumology/ID/ICU	Prospective	8 / 32	20.0	Death vs survival	Not reported	Mean (SD)	High	-0.41 (-1.19 to 0.37)
Sharma 2023[38]	India	COVID-19 (hospitalised full severity spectrum)	Tertiary hospital inpatient	Prospective	10 / 135	6.9	Death vs discharge	25.4	Mortality AUC	Moderate	1.95 (0.85 to 3.05)
Daorattanachai 2023[39]	Thailand	COVID-19	Inpatient ward	Retrospective	26 / 224	10.4	28-day mortality	25	Mortality AUC	Moderate	0.51 (0.05 to 0.96)
Bajic 2023[40]	Serbia	COVID-19 sepsis	ICU	Retrospective	106 / 54	66.2	28-day mortality	26	Mean (SD)	Moderate	0.50 (0.17 to 0.83)
Frugoli 2023[41]	USA	COVID-19	Inpatient (27.5% ICU)	Retrospective	47 / 284	14.2	In-hospital death	24.9	2 × 2 odds ratio	Moderate	0.70 (0.34 to 1.05)
Agnello 2024[42]	Italy	Critically ill incl. sepsis	ICU	Prospective	41 / 45	47.7	ICU / intra-hospital mortality	36	2 × 2 odds ratio	Low	0.58 (-0.11 to 1.28)
Chandrabhatla 2024[43]	India	Sepsis	ICU tertiary care	Prospective	8 / 76	9.5	In-hospital mortality	21.86	Mortality AUC	Moderate	-0.30 (-1.02 to 0.42)
Lai 2025[44]	Taiwan	COVID-19 pneumonia	Inpatient	Retrospective	132 / 746	15.0	In-hospital mortality	22	2 × 2 odds ratio	Low	0.57 (0.34 to 0.79)
Theodoridis 2025[45]	Greece	Sepsis	Emergency department (2 centres)	Prospective	34 / 34	50.0	In-hospital death	29.3	Mean (SD)	Moderate	0.78 (0.29 to 1.27)
Arsenijevic 2026[46]	Serbia	Surgical sepsis	Two surgical ICUs	Prospective	24 / 36	40.0	In-hospital mortality	29.95	Mortality AUC	Moderate	0.70 (0.11 to 1.29)

Two features of the included set require comment before the pooled results are presented. First, monocyte distribution width was reported in arbitrary units by most studies and in femtolitres by one. These conventions are not interchangeable labels for an identical scale, because the reported value depends on analyser calibration as well as on the underlying biology, and this is one of the reasons a standardised rather than a raw mean difference was chosen. Second, the nine-fold spread in cohort mortality shown in the seventh column of Table 1 reflects genuinely different clinical populations. What these cohorts share, and what makes pooling defensible, is the contrast being estimated rather than the population in which it is estimated: in every case the quantity synthesised is the within-cohort difference in monocyte distribution width between those who died and those who survived. A standardised mean difference is expressed relative to each cohort's own dispersion and is therefore not driven by differences in baseline risk between cohorts. The meta-regression on cohort mortality rate, reported in *Subgroup analyses and meta-regression*, provides the empirical test of this reasoning and was null.

Risk of bias

Overall risk of bias was rated low in two studies, moderate in nine and high in one. Study confounding was by a substantial margin the weakest domain: seven of the twelve studies reported no multivariable adjustment for illness severity, despite Sequential Organ Failure Assessment or Acute Physiology and Chronic Health Evaluation II scores differing markedly between survivors and non-survivors within those same cohorts. Prognostic factor measurement was the strongest domain, reflecting the fact that monocyte distribution width is generated automatically by a standard haematology analyser without operator input; the one systematic concern in this domain was pre-analytical, in that the choice between dipotassium and tripotassium ethylenediaminetetraacetic acid collection tubes shifts monocyte distribution width materially and was left

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unreported in almost every study. The single study rated at high risk overall[37] reported outcome data for only 40 of 60 enrolled patients and had a non-survivor group of only eight patients. The domain-level judgements for every study are given in Table 2 and displayed graphically in Figure 2.

Table 2. Domain-level risk-of-bias judgements for the twelve included studies using the Quality In Prognosis Studies tool. The same judgements are displayed graphically in Figure 2.

Study	D1 Participation	D2 Attrition	D3 Prognostic factor	D4 Outcome	D5 Confounding	D6 Analysis and reporting	Overall
Riva 2021 (Italy)[35]	Moderate	Low	Low	Moderate	High	Moderate	Moderate
Lorubbio 2022 (Italy)[37]	High	High	Low	Moderate	High	High	High
Soo 2022 (Malaysia)[36]	Low	Low	Low	Low	Low	Moderate	Moderate
Sharma 2023 (India)[38]	Moderate	Low	Low	Moderate	High	Moderate	Moderate
Daorattanachai 2023 (Thailand)[39]	Moderate	Low	Low	Low	High	Moderate	Moderate
Bajic 2023 (Serbia)[40]	Moderate	Low	Moderate	Low	High	Moderate	Moderate
Frugoli 2023 (USA)[41]	Moderate	Low	Moderate	Low	High	Moderate	Moderate
Agnello 2024 (Italy)[42]	Low	Moderate	Low	Low	Low	Low	Low
Chandrabhatla 2024 (India)[43]	Moderate	Low	Low	Moderate	High	Moderate	Moderate
Lai 2025 (Taiwan)[44]	Low	Low	Low	Low	Low	Low	Low
Theodoridis 2025 (Greece)[45]	Low	Moderate	Low	Low	Moderate	Moderate	Moderate
Arsenijevic 2026 (Serbia)[46]	Moderate	Low	Low	Low	Moderate	Low	Moderate

Figure 2. Risk-of-bias assessment of the twelve included prognostic cohort studies using the Quality In Prognosis Studies (QUIPS) tool. Green denotes low risk, amber moderate risk and red high risk. Study confounding was the weakest domain, with seven of twelve studies reporting no multivariable adjustment for illness severity. The underlying judgements are tabulated in Table 2.

The two cohorts recovered from journals not indexed in MEDLINE[36,38] were rated at moderate overall risk of bias, which places them in the same category as nine of the twelve included studies and above the single study rated high. Neither was an outlier on any individual domain, as Table 2 shows. Their methodological quality therefore provides no basis for treating them differently from the remainder of the evidence base, and the leave-one-out analysis in *Sensitivity analyses* confirms that neither drives the pooled result.

Primary outcome: pooled standardised mean difference

Monocyte distribution width measured at or near admission was significantly higher in patients who subsequently died than in those who survived. The pooled Hedges' g was 0.60 (95% CI 0.39 to 0.80, z = 5.70, p < 0.001) across twelve cohorts and 2,289 patients. By conventional benchmarks this represents a moderate effect: the average non-survivor sat approximately six-tenths of a standard deviation above the average survivor on monocyte distribution width. Between-study heterogeneity was moderate, with $\tau^2 = 0.058$, $\tau = 0.241$, $I^2 = 50.8\%$, $H^2 = 2.03$ and Cochran Q = 22.34 on 11 degrees of

freedom (p = 0.022). The 95% prediction interval ran from 0.08 to 1.11, indicating that in a new comparable cohort the effect would be expected to remain positive but could range from trivial to large. The individual study estimates, their weights and the pooled diamond with its prediction interval are shown in Figure 3; the same per-study values appear in the final column of Table 1.

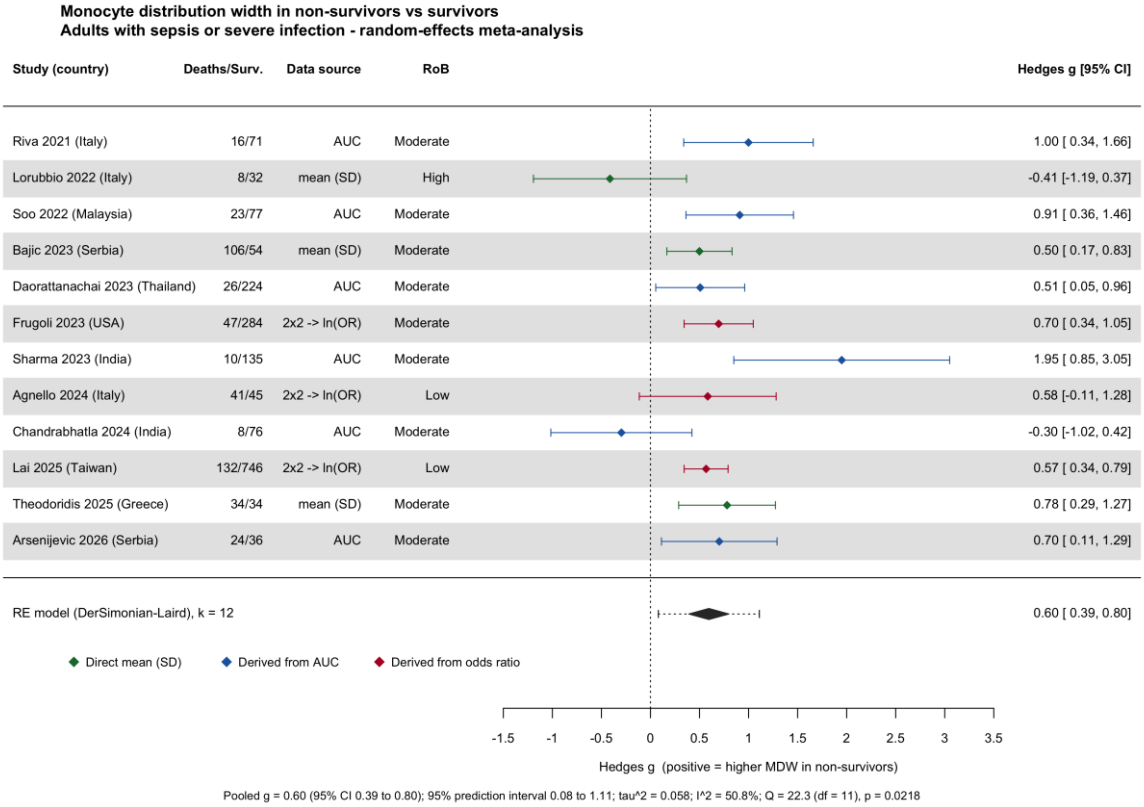

Figure 3. Forest plot of the standardised mean difference in monocyte distribution width between non-survivors and survivors. Marker colour and marker shape both encode the data source — green for a directly reported mean and standard deviation, blue for derivation from the reported mortality area under the curve, and red for derivation from a 2 × 2 mortality table — so the encoding remains legible in greyscale reproduction. The dashed whiskers on the summary diamond represent the 95% prediction interval. Numerical values for every study appear in Table 1.

As Figure 3 shows, ten of the twelve cohorts produced a positive point estimate, ranging from 0.50 in the Serbian intensive care cohort[40] to 1.95 in the Indian COVID-19 cohort;[38] the two negative estimates came from the smallest non-survivor groups, −0.41 with eight deaths[37] and −0.30 with eight deaths.[43] The pooled estimate was essentially unchanged across four different estimators of the between-study variance, ranging only from 0.59 to 0.60, and remained significant under every one of them, as detailed in Table 3. The strict subset restricted to the three studies reporting directly observed means gave a directionally consistent but non-significant estimate of 0.38 (95% CI −0.15 to 0.91, p = 0.160, I^2 = 69.1%). That model is reported deliberately in the final row of Table 3: it represents the honest limit of what the raw published means alone can support, and it is the principal justification for the harmonised three-tier approach.

Table 3. Primary pooled standardised mean difference and robustness models. The strict subset in the final row uses only the three studies that reported a mean and standard deviation by vital status.

Model	k	Hedges' g	95% CI	p	τ^2	I^2 (%)	Q (df)	p (Q)
PRIMARY — random-effects, DerSimonian–Laird	12	0.60	0.39 to 0.80	<0.001	0.058	50.8	22.34 (11)	0.022
Robustness — restricted maximum likelihood	12	0.59	0.46 to 0.72	<0.001	0.000	0.0	—	—
Robustness — Paule–Mandel	12	0.60	0.32 to 0.88	<0.001	0.163	74.3	—	—
Robustness — REML with Hartung–Knapp–Sidik–Jonkman	12	0.59	0.39 to 0.80	<0.001	0.000	0.0	—	—
Robustness — fixed-effect (common-effect)	12	0.59	0.46 to 0.72	<0.001	—	50.8	—	—
Strict subset — directly reported mean (SD) only	3	0.38	-0.15 to 0.91	0.160	0.146	69.1	6.47 (2)	0.039

One feature of Table 3 requires explanation because it may otherwise read as an inconsistency. The heterogeneity statistics differ markedly between estimators: the DerSimonian–Laird model returns I^2 = 50.8%, the restricted maximum likelihood model returns approximately zero, and the Paule–Mandel model returns 74.3%. This is a genuine and well-recognised feature of small meta-analyses rather than a computational error. I^2 is not an absolute property of a dataset but a function of the estimated between-study variance, and with twelve studies that variance is itself estimated with wide uncertainty. Restricted maximum likelihood shrinks the estimate towards zero when the likelihood surface is flat, whereas Paule–Mandel, which matches the moment condition of Cochran Q, tends to return larger values. The third column of Table 3 nonetheless shows that the pooled point estimate was almost invariant across all five models, which is the more important observation: the conclusion does not depend on how the between-study

variance is estimated, even though the apparent heterogeneity does.

Secondary outcomes

Nine studies permitted construction of a 2 × 2 table of death by monocyte distribution width above versus below the study-specific cut-off. The pooled odds ratio for mortality was 4.68 (95% CI 2.99 to 7.33, p < 0.001, I^2 = 42.0%) across 335 non-survivors and 1,504 survivors, indicating that an elevated monocyte distribution width was associated with approximately five-fold higher odds of death. This estimate must be interpreted with caution: as the cut-off column of Table 1 shows, thresholds varied from 20 to 36 units between studies and were frequently derived and tested within the same sample, which inflates apparent performance. Eight studies reported a mortality area under the receiver operating characteristic curve, and the pooled area under the curve was 0.676 (95% CI 0.598 to 0.746, I^2 = 51.7%) across 247 non-survivors and 707 survivors. Both secondary analyses are summarised in Table 4 and displayed in Figure 4.

Table 4. Secondary analyses: pooled mortality odds ratio, pooled discrimination, and the crude versus severity-adjusted comparison within the same three studies.

Secondary analysis	Scale	k	Deaths / survivors	Pooled estimate (95% CI)	I^2 (%)	p
Mortality odds ratio, elevated versus non-elevated MDW	Odds ratio	9	335 / 1,504	4.68 (2.99 to 7.33)	42.0	<0.001
Discrimination of MDW for mortality (pooled AUC)	AUC	8	247 / 707	0.676 (0.598 to 0.746)	51.7	-
Crude odds ratio in the three studies reporting an adjusted estimate	Odds ratio	3	179 / 859	3.99 (2.17 to 7.33)	40.3	<0.001
Severity-adjusted ratio in the same three studies	Adjusted OR / HR	3	179 / 859	2.68 (1.84 to 3.91)	0.0	<0.001

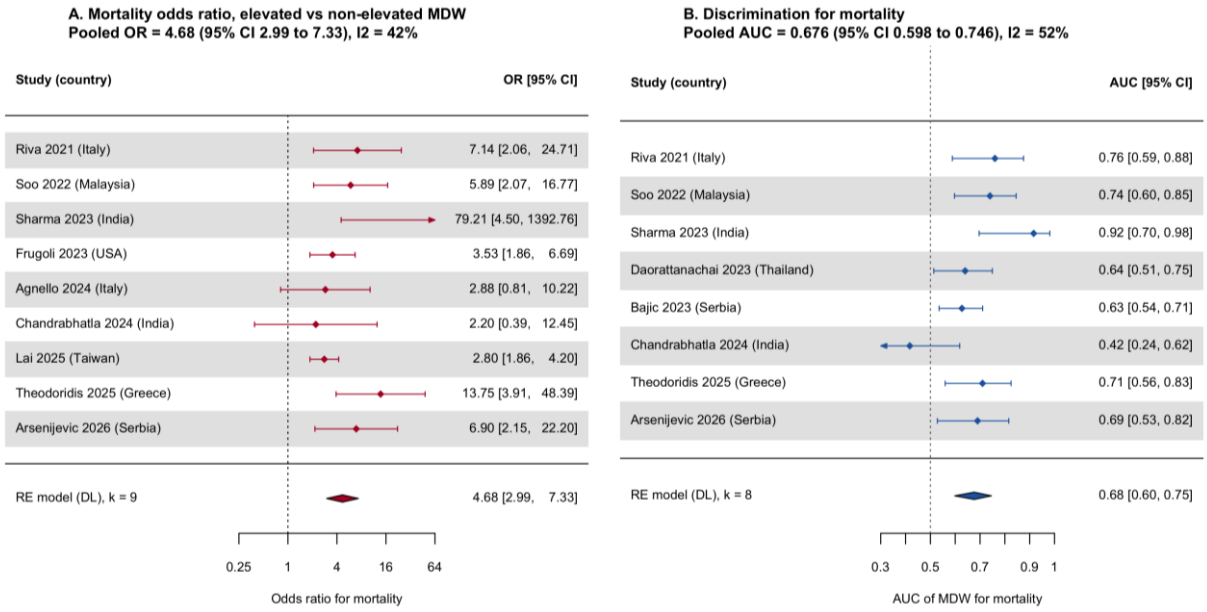

Figure 4. Secondary analyses. Panel A shows the pooled mortality odds ratio for elevated versus non-elevated monocyte distribution width. Panel B shows the pooled area under the receiver operating characteristic curve of monocyte distribution width for mortality; the dotted line marks an area under the curve of 0.5, denoting no discrimination. Pooled values are given in Table 4.

The pooled area under the curve of 0.676 shown in the second row of Table 4 and in panel B of Figure 4 is the single most important result for tempering enthusiasm about this biomarker. A value of approximately 0.68 represents modest discrimination, well below the threshold of 0.80 conventionally demanded of a stand-alone prognostic test, and below the Sequential Organ Failure Assessment score in every head-to-head comparison available within the included cohorts.

Four studies reported a severity-adjusted estimate alongside the crude association. Because this comparison carries considerable interpretative weight, the individual estimates are given in Table 5 before the pooled figure. In one intensive care cohort a crude hazard ratio of 5.89 fell to 4.08 (95% CI 1.55 to 10.75) after adjustment for age and the Sequential Organ Failure Assessment score in a Cox model, an attenuation of 37.1%, and remained significant.[36] In a large inpatient COVID-19 cohort a crude odds ratio of 2.80 fell to 2.46 (95% CI 1.63 to 3.74) after multivariable logistic adjustment that did not include a severity score, an attenuation of 18.8%, and remained significant.[44] In a surgical intensive care cohort a crude odds ratio of 6.91 fell to 3.69 (95% CI 0.34 to 40.14) after multivariable logistic adjustment that did include the Sequential Organ Failure Assessment score, an attenuation of 54.4%, and lost significance.[46] A fourth study reported a per-unit hazard ratio that fell from a crude 2.88 to an adjusted 1.05 (95% CI 1.00 to 1.11); because this is expressed on a per-unit rather than a dichotomised scale it is not commensurable with the other three and was not pooled.[42]

Table 5. Crude and severity-adjusted estimates in the four studies reporting both. The fourth study reports a per-unit hazard ratio and was therefore not pooled with the other three.

Study	Measure	Crude estimate	Severity-adjusted estimate (95% CI)	Adjustment set	Scale of the adjusted estimate	Attenuation (%)	Remained significant
Soo 2022[36]	HR	5.89	4.08 (1.55 to 10.75)	age + SOFA (Cox)	high vs low MDW (dichotomised)	37.1	Yes
Agnello 2024[42]	HR	2.88	1.05 (1.00 to 1.11)	multivariable Cox (per 1 unit)	per 1 unit of MDW	Not applicable	No
Lai 2025[44]	OR	2.80	2.46 (1.63 to 3.74)	multivariable logistic	high vs low MDW (dichotomised)	18.8	Yes
Arsenijevic 2026[46]	OR	6.91	3.69 (0.34 to 40.14)	multivariable logistic incl. SOFA	high vs low MDW (dichotomised)	54.4	No

Pooling the three commensurable estimates, the crude pooled odds ratio of 3.99 (95% CI 2.17 to 7.33) fell to 2.68 (95% CI 1.84 to 3.91) after adjustment, as shown in the last two rows of Table 4. The excess odds were therefore reduced by approximately 44%, equivalent to 29% on the log-odds scale, and the association remained clearly significant. Two caveats must accompany this figure. The three studies adjusted for different covariate sets, as the fifth column of Table 5 makes plain, so the pooled adjusted estimate combines quantities that are not strictly identical and should be read as indicative rather than as a formal adjusted effect. The reported I^2 of 0.0% in that analysis is reassuring at face value but is essentially uninformative with three studies. The pattern across the individual estimates in Table 5 is more instructive than the pooled value: attenuation was smallest where the adjustment set excluded a severity score and largest where the Sequential Organ Failure Assessment score was included, and both of the two studies adjusting specifically for that score were the studies in which significance was lost or became borderline.

Subgroup analyses and meta-regression

Six subgroup analyses were performed and are set out in full in Table 6, with the corresponding forest plot in Figure 5. Only overall risk of bias emerged as a significant moderator ($Q = 5.605$, $df = 1$, $p = 0.018$). The single study rated at high risk of bias was the only cohort with a negative direct-data point estimate, at −0.41; excluding it raised the pooled estimate to 0.64 (95% CI 0.46 to 0.82) and lowered I^2 from 50.8% to 36.8%. The primary analysis nonetheless retained that study, because removing a cohort on the grounds that its result is inconvenient would constitute a more serious methodological error than retaining it.

Table 6. Subgroup analyses of the pooled standardised mean difference, with tests for subgroup difference. Displayed graphically in Figure 5.

Moderator	Level	k	Hedges' g (95% CI)	I^2 (%)	Test for subgroup difference
Aetiology of the septic insult	Bacterial or mixed sepsis	5	0.58 (0.21 to 0.96)	48.7	Q = 0.003, df = 1, p = 0.955
	COVID-19 / viral	7	0.60 (0.34 to 0.86)	58.5	
Level of care at sampling	ED / ward / mixed inpatient	4	0.71 (0.37 to 1.05)	53.6	Q = 0.789, df = 1, p = 0.375
	ICU	8	0.52 (0.23 to 0.80)	55.1	
Study design	Prospective	8	0.62 (0.21 to 1.03)	67.3	Q = 0.053, df = 1, p = 0.817
	Retrospective	4	0.57 (0.42 to 0.72)	0.0	
Risk of bias (QUIPS overall)	High risk of bias	1	-0.41 (-1.19 to 0.37)	—	Q = 5.605, df = 1, p = 0.018
	Low or moderate risk of bias	11	0.64 (0.46 to 0.82)	36.8	
Effect-size derivation	Converted effect estimate	9	0.66 (0.42 to 0.89)	46.3	Q = 0.991, df = 1, p = 0.320
	Directly reported mean (SD)	3	0.38 (-0.15 to 0.91)	69.1	
Derivation tier	Tier A — directly reported mean (SD)	3	0.38 (-0.15 to 0.91)	69.1	Q = 1.055, df = 2, p = 0.590
	Tier B — converted from a mortality AUC	6	0.72 (0.28 to 1.16)	65.1	
	Tier C — converted from an odds ratio	3	0.60 (0.42 to 0.79)	0.0	

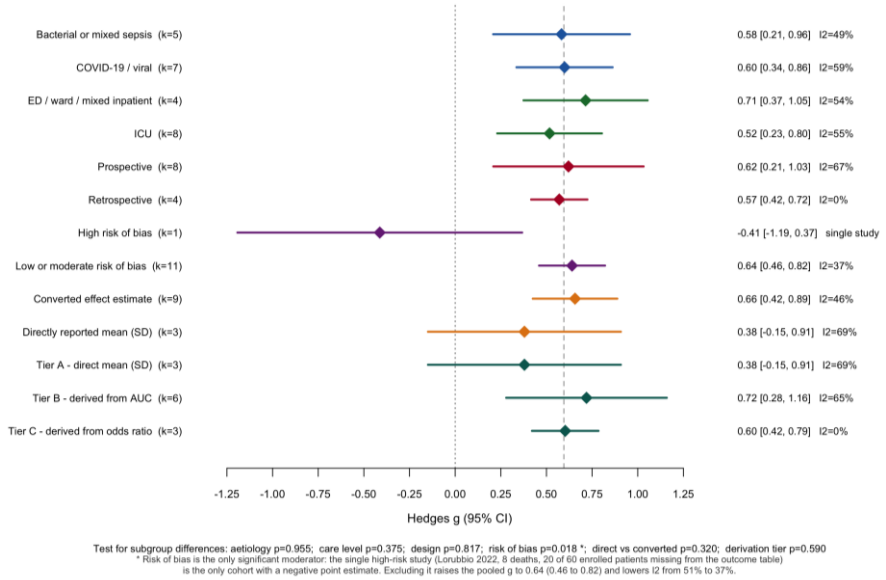

Figure 5. Subgroup analyses of the pooled standardised mean difference by aetiology of the septic insult, level of care at sampling, study design, overall risk of bias and route of effect-size derivation. Corresponding numerical estimates and tests for subgroup difference are given in Table 6.

Aetiology did not modify the effect: as the first two rows of Table 6 show, bacterial or mixed sepsis gave 0.58 (95% CI 0.21 to 0.96, k = 5) and COVID-19 or viral sepsis gave 0.60 (95% CI 0.34 to 0.86, k = 7), with p = 0.955 for the subgroup difference. This finding matters because seven of the twelve cohorts were recruited during the pandemic, and it establishes that the prognostic signal is not a COVID-19 artefact. Level of care showed a directionally interesting but statistically unsupported difference, with emergency department, ward or mixed inpatient cohorts giving 0.71 (95% CI 0.37 to 1.05, k = 4) against 0.52 (95% CI 0.23 to 0.80, k = 8) in intensive care (p = 0.375). Study design made no difference (p = 0.817).

The most important methodological subgroup analysis concerned the route by which each effect size was derived, shown in the final three rows of Table 6. Tier A gave 0.38, Tier B gave 0.72 and Tier C gave 0.60, with p = 0.590 across the three tiers, and the simpler contrast of directly reported against converted estimates gave p = 0.320. The conversions therefore did not shift the answer, although the power of that test was limited and its interpretation is qualified in *Strengths and limitations*.

None of the seven meta-regressions explained any of the between-study variance, as Table 7 documents: R^2 was 0% throughout and every p value exceeded 0.3. In particular the effect size was flat against cohort mortality rate (slope 0.0043 per 10% higher mortality, p = 0.941), so the pooled estimate was not an artefact of case-mix severity, and flat against publication year (slope −0.0162 per year, p = 0.845), so there was no sign of the diminishing-effect pattern typical of an initially over-optimistic literature. The relationship between effect size and cohort mortality is displayed graphically in panel D of Figure 6.

Table 7. Meta-regressions on study-level moderators. No moderator explained any of the between-study variance.

Moderator	k	Slope or contrast	95% CI	p	Residual I^2 (%)	R^2 explained (%)
Cohort mortality rate (per 10% higher)	12	0.0043	-0.1093 to 0.1179	0.941	55.2	0.0
Publication year (per year)	12	-0.0162	-0.1780 to 0.1457	0.845	55.1	0.0
log(total sample size)	12	0.0423	-0.2169 to 0.3016	0.749	55.2	0.0
COVID-19 vs bacterial/mixed sepsis	12	0.0129	-0.4339 to 0.4596	0.955	55.1	0.0
ICU vs ED/ward	12	-0.2091	-0.6705 to 0.2524	0.375	54.7	0.0
Retrospective vs prospective	12	-0.0509	-0.4829 to 0.3811	0.817	54.8	0.0
Converted vs direct effect size	12	-0.2465	-0.7320 to 0.2389	0.320	53.2	0.0

Sensitivity analyses

Twelve leave-one-out models were fitted and are reported individually in Table 8. The pooled estimate remained between 0.561 and 0.642 and remained statistically significant in every one, with the lowest confidence interval lower bound across all models being 0.350. No study was flagged as influential by the standard criteria of studentised residuals, DFFITS, Cook's distance or hat values; the largest Cook's distance was 0.1998, well below the conventional 4/k threshold of 0.333. The Baujat plot in panel A of Figure 6 identified two heterogeneity drivers, both small cohorts with negative point estimates,[37,43] and panel B confirms that neither dominated the analysis.

Table 8. Leave-one-out analysis with influence diagnostics. The conventional threshold for Cook's distance at k = 12 is 0.333; no study exceeded it.

Study omitted	k remaining	Pooled g	95% CI	I^2 (%)	Studentised residual	Cook's distance	Influential
Riva 2021[35]	11	0.568	0.356 to 0.780	52.0	1.006	0.0690	No
Soo 2022[36]	11	0.568	0.352 to 0.784	52.3	0.880	0.0691	No
Lorubbio 2022[37]	11	0.640	0.459 to 0.821	36.8	-2.368	0.1842	No
Sharma 2023[38]	11	0.561	0.379 to 0.743	39.0	2.323	0.1057	No
Daorattanachai 2023[39]	11	0.605	0.379 to 0.832	55.0	-0.265	0.0087	No
Bajic 2023[40]	11	0.609	0.375 to 0.843	54.6	-0.318	0.0166	No
Frugoli 2023[41]	11	0.582	0.350 to 0.814	54.5	0.327	0.0156	No
Agnello 2024[42]	11	0.596	0.377 to 0.815	55.2	-0.027	0.0001	No
Chandrabhatla 2024[43]	11	0.642	0.457 to 0.827	38.7	-2.228	0.1998	No
Lai 2025[44]	11	0.600	0.352 to 0.849	55.1	-0.096	0.0022	No
Theodoridis 2025[45]	11	0.577	0.355 to 0.799	54.0	0.540	0.0307	No
Arsenijevic 2026[46]	11	0.587	0.366 to 0.808	55.0	0.278	0.0065	No
None (full model)	12	0.595	0.391 to 0.800	50.8	—	—	—

Fourteen restricted and alternative models were fitted and are listed in Table 9. Every restriction except the three-study direct-means-only model produced a significant positive pooled effect between 0.561 and 0.657. Removing the single largest cohort, which contributed 878 patients,[44] changed the pooled estimate by 0.005. Restricting the analysis to studies reporting at least ten deaths produced the tightest result obtained anywhere in this review, at 0.654 (95% CI 0.517 to 0.792) with I^2 of only 4.2%, which localises the residual heterogeneity to imprecise small studies rather than to genuine clinical disagreement between settings. The cumulative meta-analysis in panel C of Figure 6 shows the pooled estimate stabilising close to its final value from 2023 onwards.

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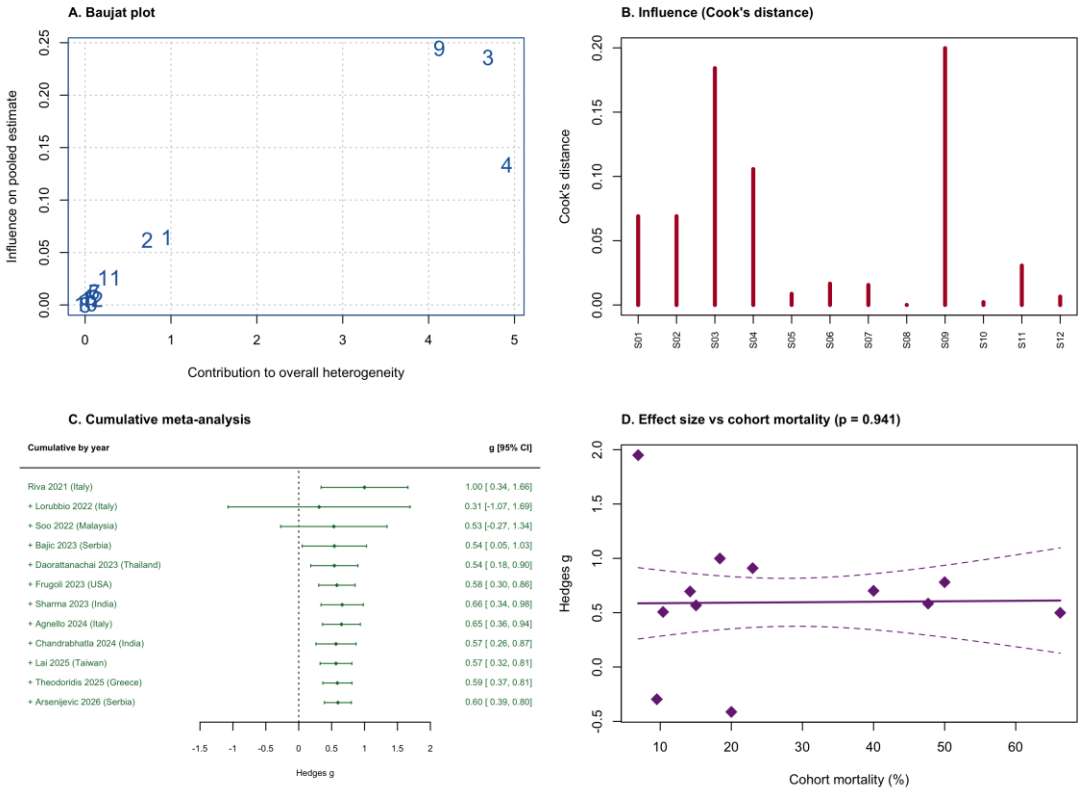

Figure 6. Influence and stability diagnostics. Panel A is a Baujat plot of the contribution of each study to overall heterogeneity against its influence on the pooled estimate. Panel B shows Cook's distance by study, with the dashed line marking the conventional 4/k threshold. Panel C shows the cumulative meta-analysis ordered by year of publication. Panel D plots effect size against cohort mortality with the meta-regression line. Panels B and D are those most directly interpretable by a clinical readership; panels A and C are technical diagnostics retained for methodological completeness.

Table 9. Restricted and alternative models (sensitivity analyses).

Restricted or alternative model	k	Pooled g	95% CI	I^2 (%)
Full model (reference)	12	0.595	0.391 to 0.800	50.8
Directly reported mean (SD) only	3	0.379	-0.149 to 0.908	69.1
Converted estimates only	9	0.656	0.425 to 0.888	46.3
Bacterial / mixed sepsis only	5	0.583	0.208 to 0.957	48.7
COVID-19 / viral only	7	0.599	0.335 to 0.863	58.5
Prospective designs only	8	0.621	0.209 to 1.032	67.3
Excluding the high-risk-of-bias study (Lorubbio 2022)	11	0.640	0.459 to 0.821	36.8
Excluding the largest cohort (Lai 2025)	11	0.600	0.352 to 0.849	55.1
Excluding studies with <10 deaths	10	0.654	0.516 to 0.792	4.2
Excluding the mild/asymptomatic-spectrum cohort (Sharma 2023)	11	0.561	0.379 to 0.743	39.0
REML variance estimator	12	0.590	0.462 to 0.718	0.0
REML + Hartung-Knapp-Sidik-Jonkman	12	0.590	0.385 to 0.795	0.0
Paule-Mandel variance estimator	12	0.598	0.317 to 0.878	74.3
Fixed-effect (common-effect) model	12	0.590	0.462 to 0.718	50.8

Small-study effects and publication bias

Because twelve studies contributed to the primary analysis, formal assessment of small-study effects was mandatory and was performed in full, as summarised in Table 10. Egger regression was not significant (t = 0.20, df = 10, p = 0.846). The Begg rank correlation test was likewise not significant (Kendall τ = 0.09, p = 0.737), although with twelve studies that test has low power and its result should be read as uninformative rather than as evidence that bias is absent. The trim-and-fill procedure imputed two studies on the left-hand side of the funnel, that is, on the side corresponding to smaller or negative effects, which is the pattern expected if small studies reporting null results had been under-published; the adjusted pooled estimate fell to 0.52 (95% CI 0.30 to 0.74) and remained significant. The Rosenthal fail-safe N was 297. The contour-enhanced funnel plot and its trim-and-fill adjusted counterpart are shown in Figure 7.

Table 10. Assessment of small-study effects and publication bias. Funnel plots are shown in Figure 7.

Test	Result	Interpretation
Egger regression (standard error as predictor)	t = 0.20, df = 10, p = 0.846	No funnel asymmetry for the primary outcome
Begg rank correlation	Kendall τ = 0.09, p = 0.737	No rank association; low power at k = 12, so uninformative rather than evidence of absence
Trim-and-fill (R_0 estimator)	2 studies imputed; adjusted g = 0.52 (0.30 to 0.74)	Two studies imputed on the left of the funnel; the adjusted estimate remained significant
Rosenthal fail-safe N	N = 297	Liberal statistic assuming a mean null effect among unpublished studies; reported for completeness
Egger regression, secondary odds-ratio outcome	p = 0.027	Significant small-study effects; the pooled odds ratio is an upper bound

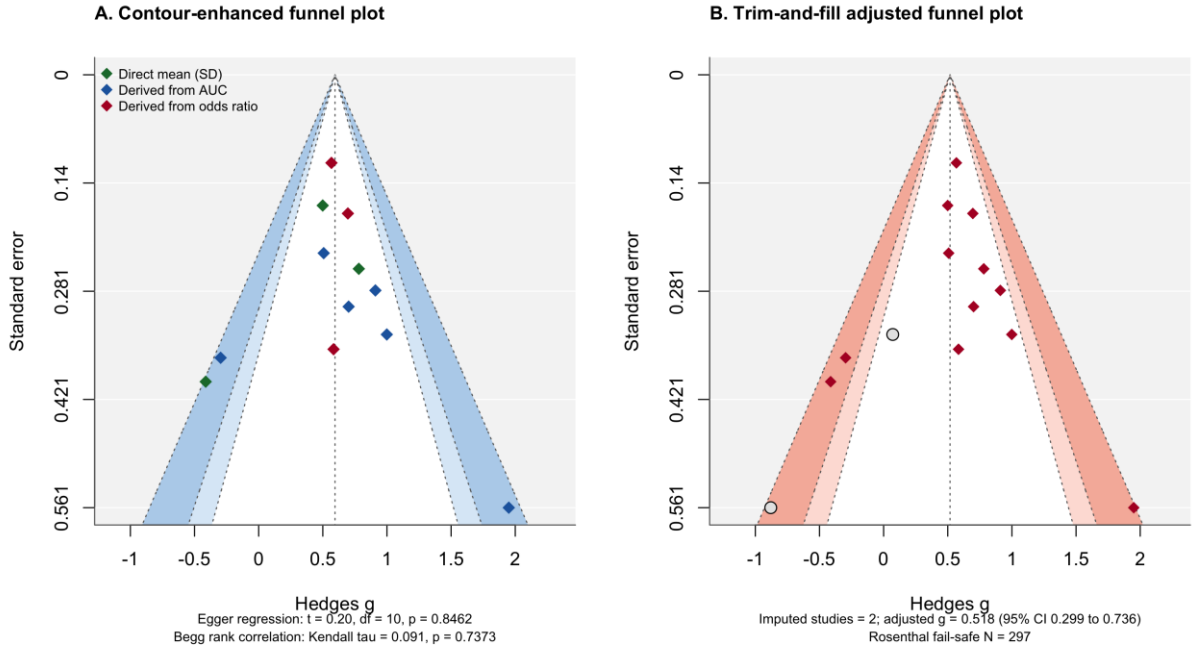

Figure 7. Contour-enhanced funnel plot for the primary outcome (Panel A) and the trim-and-fill adjusted funnel plot with two imputed studies (Panel B). The corresponding formal tests are reported in Table 10.

Egger regression applied to the secondary odds-ratio outcome was, by contrast, significant (p = 0.027), as recorded in the final row of Table 10. This divergence is informative rather than contradictory. The odds ratios depend on study-specific cut-offs that were in most cases optimised within the same sample in which they were evaluated, whereas the standardised mean difference does not depend on any threshold. This is a positive reason to treat the standardised mean difference as the primary estimate and to regard the pooled odds ratio of 4.68 as an upper bound.

Exploratory analysis of measurement timing

One included study reported serial monocyte distribution width by vital status.[45] As Table 11 shows, the separation between survivors and non-survivors widened markedly over the first five days, from a Hedges' g of 0.781 on day 1 to 1.872 on day 3 and 2.465 on day 5, with the reported area under the curve rising from 0.71 to 0.92 and then 0.94. Three further reports point in the same direction. These values must not be read as prognostic performance estimates. They are affected by survivor-depletion bias of a severe kind: as the second column of Table 11 makes explicit, the non-survivor group available for repeat sampling fell from 34 patients on day 1 to 10 on day 3 and 9 on day 5, precisely because patients died, so the day-5 comparison contrasts the survivors of the whole cohort against the small minority of eventual non-survivors who lived long enough to be sampled a third time. Any estimate constructed on that basis is conditioned on survival to the point of measurement and is therefore inflated by an unknown amount. These values are presented as exploratory and hypothesis-generating only, were excluded from every pooled analysis, and only the day-1 value from that study entered the primary model.

Table 11. Exploratory analysis of measurement timing in the single study reporting serial monocyte distribution width by vital status. Later timepoints are affected by survivor-depletion bias and were excluded from all pooled analyses.

Day of sampling	Deaths / survivors sampled	MDW in non-survivors, mean (SD)	MDW in survivors, mean (SD)	Hedges' g (95% CI)	Reported AUC	Caveat
Day 1	34 / 34	29.75 (5.38)	26.19 (3.42)	0.781 (0.287 to 1.275)	0.71	Enters the primary analysis
Day 3	10 / 31	31.79 (3.49)	25.36 (3.33)	1.872 (1.053 to 2.691)	0.92	Survivor depletion; exploratory only
Day 5	9 / 33	34.29 (5.40)	24.14 (3.62)	2.465 (1.559 to 3.371)	0.94	Survivor depletion; exploratory only

Certainty of the evidence

Certainty of the evidence was rated as low overall using the GRADE framework adapted for prognostic factor studies, with the domain-by-domain reasoning set out in Table 12. The body of evidence began at moderate certainty because it consisted entirely of prognostic cohort studies. It was downgraded one level for risk of bias, principally because seven of twelve studies made no adjustment for illness severity, and one further level for indirectness, because seven of twelve cohorts were COVID-19 cohorts, mortality timepoints varied between studies, and no cohort originated from Indonesia or a comparable health system. No downgrade was applied for inconsistency, imprecision or publication bias in relation to the primary outcome.

Table 12. Certainty of the evidence assessed with GRADE adapted for prognostic factor studies.

GRADE domain	Rating	Reason
Starting certainty	Moderate	The body of evidence consisted entirely of prognostic cohort studies, which start at moderate certainty under the GRADE prognosis framework
Risk of bias	Downgrade one level	Seven of twelve studies made no adjustment for illness severity; one study was rated at high risk overall; cut-offs were frequently derived and tested within the same sample
Inconsistency	No downgrade	I^2 was 50.8% and all subgroup and meta-regression tests were null except risk of bias; every leave-one-out model remained significant
Indirectness	Downgrade one level	Seven of twelve cohorts were COVID-19 cohorts; mortality timepoints differed; no cohort originated from Indonesia or a comparable health system
Imprecision	No downgrade	475 deaths among 2,289 patients; the 95% confidence interval excluded the null across all twelve leave-one-out models
Publication bias	No downgrade for the primary outcome	Egger p = 0.846, Begg p = 0.737 and a fail-safe N of 297; a downgrade would apply to the secondary odds-ratio outcome
OVERALL CERTAINTY	LOW	The association was consistent and unlikely to reflect chance, but confounding by severity and indirectness of the population mean that the magnitude should not be relied upon for individual clinical decisions

4. Discussion

Principal findings

This review provides the first quantitative synthesis of monocyte distribution width as a prognostic rather than a diagnostic biomarker in adults with sepsis or severe infection. Across twelve cohorts and 2,289 patients with vital-status data, monocyte distribution width measured at or near admission was moderately but consistently higher in patients who subsequently died, with a pooled Hedges' g of 0.60 (95% CI 0.39 to 0.80) as shown in Figure 3 and Table 3. The finding was robust: it survived all twelve leave-one-out models in Table 8, thirteen of the fourteen restricted models in Table 9, four different variance estimators and formal correction for small-study effects. An elevated monocyte distribution width was associated with approximately five-fold higher odds of death, and roughly seven-tenths of that association on the log-odds scale persisted after adjustment for age, sex and a severity score.

Three findings temper that headline. First, pooled discrimination was modest, at an area under the curve of 0.676, comfortably below the standard usually required of a stand-alone prognostic test. Second, a substantial share of the crude association was shared with illness severity, and the two studies in Table 5 that adjusted specifically for the Sequential Organ Failure Assessment score were the two in which statistical significance was lost or became borderline. Third, no consensus cut-off emerged; the twelve studies used thresholds spanning 21.86 to 36 units in the primary analysis, most derived and tested within the same sample, and the secondary odds-ratio analysis built upon those thresholds was the one analysis in this review that showed significant small-study effects.

What an effect size of 0.60 means at the bedside

A standardised mean difference of 0.60 is readily interpreted by statisticians and almost meaningless to most clinicians, so it is worth translating. Under the assumption of approximately normal distributions with similar variances, a Hedges' g of 0.60 corresponds to a probability of superiority of approximately 0.66: if one patient who died and one who survived were drawn at random from the pooled population, the patient who died would have the higher monocyte distribution width on roughly two occasions out of three. Put differently, the distributions of the two groups overlap by approximately three-quarters, and the average non-survivor sits at about the 73rd percentile of the survivor distribution. In the raw units reported by the three studies contributing direct means, the difference between groups was of the order of two to three units of monocyte distribution width against within-group standard deviations of three to five units, as can be read directly from Table 11 for the day-1 comparison.

These figures are the honest translation of the headline result, and they explain why the pooled area under the curve in Table 4 was only 0.676. A difference that separates group averages reliably can nonetheless leave the great majority of individual patients in a region where the two distributions overlap. This is the central reason why monocyte distribution width cannot function as a stand-alone prognostic test, and it is a more informative statement of the limitation than any threshold-based accuracy metric.

Comparison with previous meta-analyses

All previous quantitative syntheses of monocyte distribution width have addressed diagnosis rather than prognosis. The earliest pooled diagnostic accuracy for early sepsis detection and reported good sensitivity with moderate specificity.[16] Subsequent syntheses compared monocyte distribution width head-to-head against procalcitonin and C-reactive protein,[5,18] examined its performance as a marker of infection more broadly,[17] and updated the diagnostic estimate in emergency department and intensive care populations.[19,20] A separate strand addressed COVID-19.[21,22] None of these reviews addressed whether monocyte distribution width predicts death among patients who already have sepsis, and none reported a pooled prognostic effect size. The present work therefore does not update or contradict the existing literature; it answers an adjacent question that had been left open.

The one comparable published estimate arises from a meta-analysis of inflammatory biomarkers in COVID-19, which recovered only three studies for the identical contrast of monocyte distribution width between survivors and non-survivors and reported a standardised mean difference of 0.83 (95% CI 0.18 to 1.48).[23] That estimate is consistent in direction and magnitude with the present pooled result and, importantly, its k of three independently confirms that the scarcity of directly reported group means in this literature is

a structural feature rather than a failure of the present search. It is precisely that scarcity which motivated the three-tier derivation strategy adopted here and which produced the k = 3 model in the last row of Table 3.

Two further comparisons are instructive. The diagnostic areas under the curve reported for monocyte distribution width in emergency department populations typically fall between 0.75 and 0.88,[9-11,47] whereas the pooled prognostic area under the curve obtained here was 0.676. Monocyte distribution width is therefore a distinctly better diagnostic marker than prognostic marker, which is biologically coherent: monocyte anisocytosis reflects the presence and intensity of early innate immune activation, not the downstream organ dysfunction that ultimately determines survival. Comparison with procalcitonin points the same way, in that procalcitonin has likewise proved a more reliable indicator of infection than of outcome.[5,6]

Independent prognostic factor or proxy for illness severity?

This is the central unresolved question raised by the present synthesis, and it deserves a direct answer rather than a hedged one. The available evidence is genuinely compatible with two interpretations, and the data assembled here cannot adjudicate decisively between them.

The interpretation favourable to monocyte distribution width is that it carries independent prognostic information. Supporting it: the pooled adjusted odds ratio of 2.68 in Table 4 remained clearly significant, roughly seven-tenths of the crude log-odds association persisted after adjustment, the meta-regression on cohort mortality rate in Table 7 was flat, and the pooled effect did not differ between intensive care cohorts with high baseline severity and emergency department or ward cohorts with much lower severity. If monocyte distribution width were merely a restatement of organ dysfunction, an association with cohort-level severity would be expected, and none was found.

The interpretation unfavourable to monocyte distribution width is that it is largely a proxy for the severity of the underlying illness. Supporting it, and this evidence should not be minimised: seven of twelve studies performed no adjustment at all, so the crude pooled estimate is essentially unadjusted; among the four studies in Table 5 that did adjust, the two that included the Sequential Organ Failure Assessment score specifically are the two in which the association was lost or became borderline; the adjusted pooled estimate rests on only three studies using non-identical covariate sets; and in every direct comparison available, the Sequential Organ Failure Assessment score out-discriminated monocyte distribution width for death. If a marker adds nothing to a score that is already calculated at the bedside, its independent value is questionable whatever the crude association shows.

Weighing these, the most defensible position is that monocyte distribution width probably retains some prognostic information independent of organ dysfunction, but that the magnitude of that independent contribution is small, is not established, and may be negligible once a formal severity score is available. Readers should not take the pooled crude estimates in this review as evidence of independence. The proposition that monocyte distribution width is a partially redundant marker of severity remains fully consistent with everything reported here, and the burden of proof lies with those who would claim otherwise. Resolving this requires prospective cohorts that report the marker alongside a validated severity score with adjustment as a pre-specified analysis, and until such studies exist the question should be described as open.

The predominance of pandemic-era COVID-19 cohorts

Seven of the twelve included cohorts studied patients with COVID-19, most recruited during 2020 and 2021. The aetiology subgroup analysis in Table 6 found no difference between viral and bacterial cohorts, with p = 0.955 for the subgroup contrast. That result is reassuring, but it should not be over-read: the comparison involved five studies against seven, has correspondingly low power, and a non-significant subgroup test cannot establish equivalence.

More importantly, the question is substantive as well as statistical. Pandemic-era COVID-19 differed from community-acquired bacterial sepsis in ways that could plausibly alter the relationship between monocyte anisocytosis and death. The pattern of organ involvement was dominated by hypoxaemic respiratory failure rather than by the distributive shock and multi-organ dysfunction typical of bacterial sepsis. Therapeutic practice changed rapidly and profoundly within the recruitment windows of the included studies: systemic corticosteroids and interleukin-6 receptor blockade became standard of care partway through, and both directly modulate monocyte activation, which is the very biology that monocyte distribution width measures. Ventilation thresholds, prone positioning practice and the availability of intensive care beds all shifted within the same period. A cohort recruited across such changes is not a homogeneous population.

Set against this, three considerations support transportability. The biological substrate of monocyte distribution width is pathogen-independent innate immune activation rather than any pathogen-specific response, which is the mechanistic reason its diagnostic performance has proved similar in bacterial, viral and fungal sepsis and in patients living with HIV.[13] The five non-COVID-19 cohorts, which included bacterial and surgical sepsis populations, produced a pooled estimate of 0.58, almost identical to the 0.60 obtained from the COVID-19 cohorts, as Table 6 shows. And the meta-regression on publication year in Table 7 was flat, which would not be expected if a pandemic-specific phenomenon were driving the result. The reasonable conclusion is that the association is unlikely to be a COVID-19 artefact, but that the evidence base remains weighted towards a clinical context that no longer exists in the form in which it was studied, and that confirmation in contemporary bacterial sepsis cohorts is required.

Why no clinical threshold can be recommended

The single most practically limiting finding of this review is the absence of any usable threshold, and the implication is more serious than it may first appear. The pooled odds ratio of 4.68 compares patients above a cut-off with patients below it. Without a defensible cut-off, that number cannot be applied to an individual patient at all, because there is no principled basis on which to classify that patient's value as elevated. The most memorable and clinically usable-looking result in this review is therefore also the least clinically applicable, and readers should treat it as a summary of association strength in the literature rather than as a decision rule.

Two distinct causes underlie the absence of a threshold, and both must be addressed before one can be recommended. The first is methodological: the thresholds listed in Table 1 were in most cases derived by maximising the Youden index within the same sample in which they were then evaluated, which guarantees optimistic performance and produces cut-offs that do not replicate. This is also the reason the secondary odds-ratio analysis was the only analysis in this review to show significant funnel asymmetry, at p = 0.027 in Table 10, whereas the threshold-free standardised mean difference showed none.

The second cause is pre-analytical and has not previously been connected to the threshold problem, although it should be. Monocyte distribution width values depend materially on the anticoagulant used, with K_3-ethylenediaminetetraacetic acid yielding systematically higher values than the K_2 salt, and they depend further on analyser platform and calibration. A threshold derived in one laboratory may therefore fail to transfer to another even if it had been derived and validated impeccably. One included report attributed a cut-off discrepancy with another cohort explicitly to this difference.[24] Tube type was unreported in almost every included study. Any future attempt to establish a transferable threshold must therefore report the anticoagulant and analyser used, derive the threshold in one sample and validate it in another, and specify the value separately by tube type.

Serial measurement: the most promising direction

The exploratory timing data in Table 11 are, in the authors' view, the most clinically interesting material in this review, and they point towards where the useful signal in this marker is most likely to lie. In the single included study reporting serial values by vital status,[45] the separation between survivors and non-survivors widened from a Hedges' g of 0.781 on day 1 to 2.465 on day 5, and the reported area under the curve rose from 0.71 to 0.94. Three further reports, including one of the six that could not be retrieved in full, describe the same pattern, and one reported that admission values did not predict death whereas the trajectory did.[26,27]

The biological rationale is coherent. A monocyte population that remains heterogeneous after several days of source control and antimicrobial therapy plausibly indicates persistent, unresolving immune dysregulation, whereas a single admission reading captures only the intensity of the initial response and cannot distinguish a vigorous appropriate response from a dysregulated one. On this reasoning, the failure of monocyte distribution width to resolve would be the informative event, not its initial elevation.

This hypothesis cannot be tested with the present data, and the reason is important. The apparent strengthening of the effect over time is confounded by survivor depletion: as the second column of Table 11 shows, the non-survivor group available for sampling shrank from 34 patients to 9 across five days precisely because patients died, so later comparisons are conditioned on survival to the point of measurement. A naive analysis of serial values will systematically overstate prognostic performance. Answering the question properly requires a study design that handles this explicitly. Joint modelling of the longitudinal biomarker trajectory and the time-to-event outcome is the natural approach, since it estimates the association between the underlying trajectory and the hazard of death without conditioning on survival to any fixed timepoint. Landmark analysis at a pre-specified day, with all patients alive at that landmark included regardless of subsequent outcome, is a simpler and more accessible alternative.

What this review reveals about the primary literature

Two observations arising from this synthesis are findings about the state of the field rather than limitations of the present work, and they are stated as such. First, only three of twelve studies reported monocyte distribution width as a mean and standard deviation stratified by vital status, as the effect-source column of Table 1 records. A literature in which the most elementary descriptive statistic is unavailable in three-quarters of reports has a reporting problem, and it is that problem which necessitated the three-tier derivation strategy adopted here. The scarcity is structural rather than a search failure: an independent meta-analysis of inflammatory biomarkers recovered only three studies for the identical contrast.[23] Journals and authors could remedy this at no cost by requiring that biomarker values be tabulated by outcome status.

Second, seven of twelve studies of a prognostic marker performed no multivariable adjustment for illness severity, as the study-confounding column of Table 2 records, despite reporting within the same papers that severity scores differed markedly between survivors and non-survivors. For a prognostic factor study this is a fundamental omission, not a refinement, because the entire clinical question is whether the marker adds information beyond what is already known at the bedside. This is framed here as a call to the research community rather than merely as a caveat about the present analysis: routine adjustment for a validated severity score should be regarded as a minimum standard for any future study of monocyte distribution width as a prognostic marker.

Strengths and limitations

This review has several strengths. The search was exhaustive rather than sampled, with every record returned by every executed query screened and no relevance cap applied, and it extended beyond MEDLINE to Europe PMC and CrossRef, which recovered two eligible cohorts that a PubMed-only search would have missed.[36,38] No value was imputed; every number was traced to a source full text. The harmonisation strategy was pre-specified, arithmetically validated against published effect estimates, and then formally tested as a moderator, so that its adequacy is demonstrated rather than asserted. The analytical programme was unusually thorough for a review of this size, comprising the twelve leave-one-out models in Table 8, the fourteen restricted models in Table 9, the six subgroup analyses in Table 6, the seven meta-regressions in Table 7, the influence diagnostics in Figure 6 and the four assessments of small-study effects in Table 10. Finally, studies reporting null or negative findings were deliberately retained, so that the pooled estimate reflects the literature as it stands rather than a selected subset of it.

The limitations are grouped below into those affecting internal validity, which bear on whether the pooled estimate is correct for the studies included, and those affecting generalisability, which bear on whether it applies elsewhere. Within each group they are ordered by the authors' assessment of importance.

Limitations affecting internal validity. First and most importantly, residual confounding by illness severity cannot be excluded, for the reasons set out in *Independent prognostic factor or proxy for illness severity?*; seven of twelve studies performed no adjustment, the pooled adjusted estimate rests on three studies with non-identical covariate sets, and the two studies adjusting specifically for organ dysfunction were those in which the association weakened most. Second, nine of the twelve effect sizes were converted rather than computed from reported group means, and these conversions depend on distributional assumptions that cannot be verified from aggregate data; the subgroup test across derivation tiers was non-significant but had low power, with three, six and three studies in the respective tiers and point estimates ranging from 0.38 to 0.72 as Table 6 shows, so the absence of a detected difference is not evidence of equivalence. Third, the three-study analysis restricted to directly reported means did not reach statistical significance, and readers who regard only directly reported means as admissible evidence should treat the present result as hypothesis-generating. Fourth, screening was performed by a single reviewer; although every retrieved report was re-read and every numerical value independently re-extracted, the 704 titles and abstracts were screened only once, and the tests for small-study effects cannot detect a study that was never identified. Fifth, six potentially eligible reports could not be retrieved, at least two

of them large intensive care series. Sixth, risk of bias was assessed with QUIPS rather than Cochrane Risk of Bias 2.0; this is a deliberate and justified deviation, for the reasons given in *Risk-of-bias assessment*, but readers expecting the latter instrument should note it.

Limitations affecting generalisability. First, the evidence base is weighted towards pandemic-era COVID-19, which supplied seven of twelve cohorts and which differed from contemporary bacterial sepsis in organ involvement and in therapy. Second, no included cohort originated from Indonesia or a comparable South-East Asian district hospital setting, so applicability to the population the authors serve rests on assumption rather than evidence, and this is addressed separately in *Generalisability to South-East Asian district hospital practice*. Third, mortality was variously defined as intensive care unit, in-hospital, 28-day or 30-day mortality and these endpoints were pooled, as the mortality-outcome column of Table 1 records, which introduces an unquantifiable degree of outcome heterogeneity. Fourth, all included studies were observational, so the analysis speaks to association rather than to causation, and no study evaluated whether acting on a monocyte distribution width result altered patient outcomes; clinical utility therefore remains entirely untested. Fifth, the analysis was restricted to a single measurement at or near admission, whereas the exploratory data in Table 11 suggest the trajectory carries the stronger signal.

Generalisability to South-East Asian district hospital practice

Because this review makes recommendations addressed to physicians in Indonesia and comparable settings, and because no included cohort was recruited in such a setting, the tension between those two facts must be addressed rather than noted and passed over. Several features of regional practice could plausibly alter the behaviour of a marker of early innate immune activation.

Case mix differs substantially. Tuberculosis, dengue, typhoid and other tropical infections account for a considerable share of sepsis presentations regionally and are almost absent from the included cohorts. Their relevance is not merely epidemiological. Disseminated tuberculosis produces chronic rather than acute monocyte activation and may elevate monocyte distribution width without the acute deterioration the marker is intended to flag. Dengue produces marked haematological derangement including monocyte activation with concurrent thrombocytopenia and haemoconcentration, and its natural history of defervescence followed by a critical plasma-leakage phase does not map onto the trajectory assumed by any included study. Whether a marker calibrated in bacterial and COVID-19 sepsis behaves similarly in these conditions is unknown.

Timing of presentation differs, and this matters more for this marker than for most. Monocyte distribution width reflects early innate immune activation, and its measured value therefore depends on where in the illness course the patient is sampled. Where access barriers, distance and initial recourse to primary or informal care lengthen the interval from symptom onset to hospital arrival, an admission sample may be taken on the fifth day of illness rather than the first. On the trajectory evidence in Table 11 a later sample might carry a stronger rather than a weaker signal, but the direction is speculative and no included study reported time from symptom onset.

Three further differences deserve brief mention: background nutritional status, which influences the innate immune response; the prevalence of undiagnosed or poorly controlled diabetes, which modifies monocyte function; and the availability of intensive care, which affects both the case mix reaching hospital and the outcome against which the marker is measured. None of these can be quantified from the present data. The honest position is that the pooled estimate is the best available evidence for regional practice while being evidence generated elsewhere, and that a prospective regional cohort would be of considerable value.

Clinical implications and practice points

The practical case for monocyte distribution width rests on its cost and availability rather than on its discriminative power. It is generated automatically with any complete blood count performed on a compatible haematology analyser, requires no additional venepuncture, no additional reagent and no additional marginal expenditure, and is available within the turnaround time of the full blood count itself. Procalcitonin and presepsin offer no such advantage. In district and regional hospitals across Indonesia and comparable settings, where the marginal cost of an additional assay frequently determines whether it is ordered at all, a prognostic signal that arrives free with a test already being performed has a value that its area under the curve alone does not capture.

Two qualifications should accompany that case. First, the claim of no additional cost is accurate at the margin but not in aggregate: the parameter is reported only by haematology analysers equipped with volume, conductivity and scatter technology, and acquisition, servicing and any applicable licensing of such a platform represent a real institutional cost. What is free is the individual result, once the platform is in place. Second, and consequently, practical availability across district hospitals in the region depends on analyser deployment, for which the authors were unable to identify published regional data. A parameter that is free but reported only by equipment that most district hospitals do not own is of theoretical rather than practical interest, and readers should establish local analyser capability before drawing operational conclusions from this review.

A further point of interpretation belongs here rather than in the results. The 95% prediction interval for the primary outcome ran from 0.08 to 1.11. For a clinician this is arguably more informative than the confidence interval, because it describes the effect expected in a new comparable cohort rather than the precision of the average across existing ones. Its lower bound sits very close to zero. A hospital implementing monocyte distribution width reporting tomorrow should therefore expect a positive association with mortality, but should be prepared for that association to be negligible in its own population, and should not be surprised by a local audit that fails to reproduce the pooled estimate.

The following summarises how the authors would use this evidence, stated concretely so that readers are not left to infer it. A markedly elevated monocyte distribution width in an adult with confirmed or strongly suspected sepsis should be read as corroborating a clinical impression of high risk, and should prompt earlier reassessment and earlier senior review, particularly where formal severity scoring has not yet been completed or where procalcitonin is unavailable. It should not be used to reassure: a normal value in a patient who appears unwell must not lower clinical concern, because the pooled discrimination of 0.676 in Table 4 is far too weak to support a rule-out decision.

No numerical threshold is recommended, and this is a substantive answer rather than an evasion. The cut-offs used across the included studies spanned 20 to 36 units, were mostly derived and evaluated within the same sample, and are further shifted by anticoagulant and analyser platform. A physician who adopts a threshold from any single published study is adopting a number that has not been shown to transfer. Where an institution wishes to act on monocyte

distribution width systematically, the defensible approach is to establish local reference behaviour on its own analyser and tube type, and to use the parameter as a trend within a patient rather than as a fixed cut-point across patients. Monocyte distribution width should not displace or delay any element of standard sepsis care: lactate measurement, blood cultures before antimicrobials, timely broad-spectrum therapy, source control and formal severity scoring all retain priority.

Research priorities

Five priorities follow directly from the findings and from the deficiencies of the primary literature documented in *What this review reveals about the primary literature*. First, prospective cohorts should report monocyte distribution width as a mean and standard deviation stratified by vital status; the near-absence of this elementary reporting is the single largest obstacle to a definitive synthesis and could be remedied at no cost. Second, adjustment for a validated severity score should become a pre-specified minimum standard, because the independence of monocyte distribution width from illness severity is the central unresolved question and cannot be settled by further unadjusted cohorts however large. Third, serial measurement protocols should be analysed with joint models of the longitudinal marker and the time-to-event outcome, or at minimum with landmark analysis, so that the trajectory hypothesis can be tested without survivor-depletion bias. Fourth, reporting of anticoagulant tube type and analyser platform should become standard, and any proposed threshold should be derived in one sample and validated in another, with values specified separately by tube type. Fifth, a prospective cohort recruited in a South-East Asian setting, with a case mix including tuberculosis, dengue and typhoid and with time from symptom onset recorded, would address the indirectness that constitutes the principal barrier to applying this evidence locally.

5. Conclusion

This systematic review and meta-analysis of twelve observational cohorts comprising 2,289 adults with vital-status data demonstrated that monocyte distribution width measured at or near hospital admission was significantly higher in patients with sepsis or severe infection who subsequently died, with a pooled Hedges' g of 0.60 (95% CI 0.39 to 0.80, $p < 0.001$). The association was moderate and notably stable: it persisted across all twelve leave-one-out models, across thirteen of the fourteen restricted models, across four estimators of between-study variance, and after formal adjustment for small-study effects. It was not confined to COVID-19 and did not vary with cohort mortality, sample size, study design or year of publication.

An elevated monocyte distribution width carried approximately five-fold higher odds of death, and roughly seven-tenths of that association on the log-odds scale persisted after adjustment for age, sex and a severity score. Pooled discrimination was nevertheless modest, at an area under the curve of 0.676, and the Sequential Organ Failure Assessment score out-performed it in every available head-to-head comparison. Certainty of the evidence was rated low, principally because seven of twelve studies made no adjustment for illness severity and seven of twelve cohorts comprised patients with COVID-19.

The clinical inference these data will bear is limited but genuine. Monocyte distribution width should be regarded as a free, immediately available adjunct that corroborates rather than establishes elevated mortality risk, and that may be of particular value where procalcitonin and presepsin are not routinely accessible. It should not be used to reassure, and it should not displace formal severity scoring. No single threshold can presently be recommended, because published cut-offs were mostly optimised within their own derivation samples and are further shifted by anticoagulant and analyser platform.

Definitive evidence will require prospective cohorts that report monocyte distribution width as a mean and standard deviation stratified by vital status, adjust routinely for a validated severity score, record the anticoagulant tube type, and analyse serial measurements with methods accounting for survivor depletion. Whether monocyte distribution width adds prognostic information beyond an organ dysfunction score remains, on the present evidence, an open question rather than a settled one.

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Author contributions

Both authors contributed to the conception and design of the review. I Gusti Agung Made Risma Ari Pertiwi performed the literature search, study selection, data extraction and statistical analysis, and drafted the manuscript. I Komang Parwata provided methodological oversight of the laboratory and pre-analytical content, verified the extracted haematological data, and critically revised the manuscript. Both authors approved the final version and agree to be accountable for all aspects of the work.

Ethics and consent

Ethical approval and informed consent were not required, as this study was a secondary analysis of previously published aggregate data and involved no individual patient data.

Conflict of interest

The authors declare no conflict of interest.

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Data availability

All data supporting the findings of this study are contained within the article and are derived from the published reports cited in the reference list.

Use of artificial intelligence

All statistical analyses, data extraction and interpretation were performed and verified by the authors, who take full responsibility for the content.

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