

Impact of a Capillary Refill Time–Guided Personalised Hemodynamic Resuscitation Protocol in Septic Shock in Low- and Middle-Income Countries: A Post Hoc Analysis of the ANDROMEDA-SHOCK-2 Trial

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Research Article

Keywords: Septic Shock, Hemodynamic Monitoring, Capillary Refill Time, Low- and Middle-Income Countries

Posted Date: October 18th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11233082/v1>

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Abstract

PURPOSE: To assess the treatment effect of capillary refill time–guided personalised hemodynamic resuscitation (CRT-PHR) in patients with early septic shock in low- and middle-income countries (LMICs).

METHODS: Post hoc analysis of the ANDROMEDA-SHOCK-2 randomised clinical trial, conducted in 86 ICUs across 19 countries. Centres were classified according to World Bank income groups as LMICs or high-income countries (HICs). The primary outcome was a hierarchical composite of 28-day mortality, duration of vital organ support, and hospital length of stay, analysed using a stratified win ratio.

RESULTS: Among 1,467 patients, 652 (44.4%) were treated in LMIC centres and 815 (55.6%) in HIC centres. Patients enrolled in LMICs were younger, had higher lactate levels, more frequent abnormal CRT, and greater baseline vasopressin use (59.4% vs 29.5%). Treatment-effect estimates were similar across income groups, with win ratios of 1.16 (95% CI 1.14–1.18) in LMICs and 1.18 (95% CI 1.17–1.20) in HICs, with no evidence of treatment-effect modification by country income level. Within LMICs, baseline lactate >4 mmol/L showed the strongest exploratory signal of heterogeneity (win ratio 1.57 vs 0.93; interaction $p=0.002$). Vasopressin use was associated with a numerically larger treatment-effect estimate (1.39 vs 1.12), but was not statistically significant. Centre-level analyses suggested heterogeneity by hospital and ICU size (interaction $p=0.081$ for both).

CONCLUSION: Despite the marked differences in baseline severity, vasopressor use, and resuscitation practice, CRT-PHR produced consistent and significant treatment effects in both LMIC and HIC settings. Within LMICs, hyperlactatemia a centre-level heterogeneity identified contexts of differential benefit, underscoring limitations of national income classification as a proxy for local critical-care capacity.

TAKE HOME MESSAGE

In this post hoc analysis of ANDROMEDA-SHOCK-2, CRT-guided personalised hemodynamic resuscitation showed similar treatment-effect estimates across LMICs and HICs settings, despite marked differences in baseline severity and resuscitation patterns. Within LMICs, patients with lactate >4 mmol/L derived the greatest benefit, while centre-level analyses revealed that hospital ownership and ICU size better capture the institutional heterogeneity that shapes treatment response. CRT-guided treatment for septic patients is a reliable hemodynamic resuscitation strategy even in centres where resources are scarce.

BACKGROUND

Sepsis and septic shock remain leading causes of critical illness worldwide, with differences in burden between low- and middle-income countries (LMICs) and high-income countries (HICs).[1] Mortality is reported at 30–40% in LMICs versus 15–20% in HICs [1–3], with higher ICU and hospital mortality

despite similar sepsis prevalence.[4, 5] These differences may reflect limited ICU capacity, delayed presentation, restricted access to surgical source control and inadequate monitoring capabilities.[6] LMICs also have a higher prevalence of infectious disease, poor sanitation, and elevated rates of hospital-acquired and multidrug-resistant infections which may contribute to this burden. [7] Socioeconomic inequities, including lower income, limited education, lack of health insurance, and underfinanced public health systems, are further associated with increased sepsis mortality. [8, 9]

In the ANDROMEDA-SHOCK trial, capillary refill time (CRT)-targeted resuscitation resulted in less organ dysfunction at 72 hours compared with lactate-targeted resuscitation. [10] A subsequent personalised CRT-based protocol in early septic shock demonstrated a more favourable hierarchical composite outcome of 28-day mortality, duration of vital organ support, and hospital length of stay (HLOS), driven primarily by a shorter duration of vital organ support. [11] CRT-targeted fluid resuscitation has also achieved hemodynamic targets faster, with similar fluid volumes and microcirculatory effects, and demonstrated that discontinuing fluid administration when CRT achieved 3 seconds was safe. [12] Although ANDROMEDA-SHOCK showed a numerically lower 28-day mortality with CRT-targeted resuscitation, the difference was not statistical significance; a post hoc re-analysis reported a high probability of mortality benefit [13] While CRT-guided resuscitation appears to reduce organ support requirements, evidence remains limited, and its effect on mortality in LMIC populations with septic shock remains uncertain.

CRT is a simple, low-cost, and feasible resuscitation target for resource-limited settings. [14] Most CRT-based trials have been conducted in Latin American and middle-income ICUs; however, none has specifically focused on septic shock populations or isolated LMIC-specific mortality effects. [10, 15] Existing evidence suggests, but does not definitively establish, a mortality benefit, and no trial has isolated treatment effects specifically within LMIC populations. We therefore aimed to determine whether a CRT-guided resuscitation protocol reduces organ support requirements and mortality among patients with septic shock in LMICs, and to assess whether treatment effectiveness varies by country income level.

METHODS

This was a post hoc exploratory analysis of the ANDROMEDA-SHOCK-2 randomised clinical trial, an international, multicentre, open-label RCT conducted across 86 ICUs in 19 countries between March 2022 and April 2025. The design, protocol, statistical analysis plan, and primary results have been reported previously. [12, 17, 18]

Parent Trial Population and intervention

Adults with septic shock were eligible if they had suspected or confirmed infection, lactate ≥ 2.0 mmol/L, and required norepinephrine to maintain MAP ≥ 65 mmHg after $\geq 1,000$ mL of intravenous fluids, within 4 hours of shock onset. Key exclusion criteria and full eligibility criteria are reported in the parent trial.

Patients were randomised 1:1 to CRT-guided personalised hemodynamic resuscitation (CRT-PHR) or usual care. In the intervention arm, hourly CRT assessment during a 6-hour protocol guided sequential optimisation of arterial pressure, fluid responsiveness, vasopressor therapy, dobutamine, and MAP targets. Full protocol details are available elsewhere. [12]

Country Income Classification

Centres were classified according to World Bank income groups. Lower-middle-, and upper-middle-income economies were grouped as LMICs and high-income economies as HICs. LMICs included Mexico, Colombia, Argentina, India, Ecuador, and Brazil; all remaining participating countries were classified as HICs. Country classification was derived from the country code embedded in the participant identifier.

To explore heterogeneity beyond national income classification, centre-level characteristics were additionally evaluated. Hospitals were classified by ownership (public/private), university affiliation, and ICU size (≤ 15 , 16–25, or > 25 beds); country-specific analyses were also performed within LMICs. Centre characteristics were derived from trial centre information and verified institutional sources. Additional regional analyses evaluated treatment effects within Latin America according to country-income classification.

Outcomes

The primary outcome was a hierarchical composite comprising: (1) 28-day all-cause mortality, favouring survival and, among non-survivors, longer survival; (2) duration of vital organ support (vasopressors, invasive mechanical ventilation, and kidney replacement therapy) through day 28, favouring shorter duration; and (3) HLOS truncated at 28 days, favouring shorter stay.

Secondary outcomes included 28- and 90-day mortality, vital support-free days at day 28, duration of vital organ support, HLOS, and component support-free days. Baseline resuscitation patterns were also characterised.

Statistical Analysis

The primary outcome was analysed using a win ratio (WR) stratified by the median APACHE II score (cut-point 19), consistent with the parent trial randomisation strategy. [18] Intervention and control patients were compared hierarchically within each stratum according to 28-day survival, duration of vital organ support, and HLOS. The WR was calculated as total wins divided by total losses, with 95% CIs derived by log transformation and normal approximation.

Mortality was analysed using Cox proportional hazards regression adjusted for APACHE II score with the Efron method for ties. Vital support-free days were analysed using ordinal logistic regression and

reported as proportional odds ratios. Continuous variables are reported as median (IQR) and categorical variables as counts and proportions.

Treatment-effect heterogeneity was assessed using treatment-by-subgroup interaction terms. For the hierarchical outcome, interaction was evaluated using likelihood-ratio testing from ordinal models; mortality interactions were evaluated in Cox models. An interaction $p < 0.10$ was considered suggestive given the exploratory design.

Predefined sensitivity analyses included exclusion of tied pairs, alternative APACHE II tertile stratification, and Cox models with country-level frailty. Exploratory patient-level subgroup analyses evaluated baseline CRT, lactate category, vasopressin use, and number of adjunctive vasoactive agents. Additional post hoc centre-level analyses evaluated hospital ownership, university affiliation, ICU size, country, and regional income-group heterogeneity. Stratified WRs were calculated using the same APACHE II framework. No adjustment for multiplicity was performed. All analyses followed the intention-to-treat principle and were conducted in R version 4.3.3 and RStudio version 2026.01.1 + 403.

RESULTS

Among 1,467 patients, 652 were treated in LMIC centres and 815 in HIC centres; 324 and 396 patients, respectively, were allocated to CRT-PHR. HIC recruitment occurred predominantly in Europe ($n = 591$, 72.5%), followed by Latin America ($n = 182$, 22.3%), the Middle East ($n = 38$, 4.7%), and North America ($n = 4$, 0.5%).

Baseline characteristics

LMIC patients were younger than HIC patients (median age 60 [IQR 43–71] vs 69 [58–77] years) and had lower APACHE II scores (17 [12–22] vs 19 [15–24]), slightly higher SOFA scores (9 [7–11] vs 8 [7–10]), higher lactate (3.9 [3.0–5.5] vs 3.5 [2.6–5.2] mmol/L), and longer CRT (4.3 [3.0–6.0] vs 4.0 [2.5–5.0] seconds) (**Table 1**). Abnormal CRT was present in 65% and 56%, respectively, and baseline vasopressin use was substantially more frequent in LMICs (59.4% vs 29.5%). Infection-source and additional baseline characteristics are shown in **Table 1**.

Primary Outcome

CRT-PHR yielded similar treatment-effect estimates for the hierarchical primary outcome across income groups (**Table 2**, Fig. 2). The stratified WR was 1.16 (95% CI 1.14–1.18; $p < 0.001$) in LMICs and 1.18 (95% CI 1.17–1.20; $p < 0.001$) in HICs, compared with 1.16 (95% CI 1.15–1.17; $p < 0.001$) overall. There was no statistical evidence of heterogeneity in treatment effect by country income level, with a treatment-by-income interaction p -value of 0.912.

Secondary Outcomes

28-day mortality was 29.3% in both treatment arms among LMIC patients (adjusted HR 0.87, 95% CI 0.65–1.17; $p = 0.364$) and 24.2% vs 24.6% among HIC patients (adjusted HR 1.04, 95% CI 0.79–1.38; $p = 0.781$), with no evidence of treatment-by-income interaction ($p = 0.418$) (**Table 2**, Figs. 1 and 3). Vital support-free days yielded adjusted proportional ORs of 1.27 (95% CI 0.96–1.67) in LMICs and 1.30 (1.02–1.66) in HICs. By day 90, mortality was 34.0% vs 35.7% in LMICs (adjusted HR 0.86, 95% CI 0.66–1.11) and 30.6% vs 31.2% in HICs (adjusted HR 0.98, 95% CI 0.76–1.25). Additional organ-support and length-of-stay outcomes are reported in **Table 2** and **Supplementary Table S2**.

Resuscitation Patterns

Baseline norepinephrine dose and pre-randomisation fluid administration were similar between income groups (0.23 vs 0.20 $\mu\text{g/kg/min}$ and 1,500 mL in both groups, respectively), whereas vasopressin use was more frequent in LMICs (59.4% vs 29.5%; $p < 0.001$). Baseline dobutamine use did not differ significantly. Detailed resuscitation patterns are shown in **Supplementary Table S3** and Fig. 4.

Sensitivity Analysis and Exploratory Subgroup Analysis

Results were consistent across the pre-specified sensitivity analyses (**Supplementary Table S4**). Exclusion of tied comparisons and alternative APACHE II tertile stratification produced nearly unchanged win-ratio estimates, and country-level frailty did not materially alter mortality estimates.

Among exploratory patient-level subgroups, baseline CRT did not modify treatment effect. In LMIC patients, however, baseline lactate showed significant heterogeneity: the WR was 1.57 (95% CI 1.53–1.62) with lactate > 4 mmol/L and 0.93 (0.90–0.95) with lactate 2–4 mmol/L (interaction $p = 0.002$) (**Supplementary Table S1, Figure S1**). Baseline vasopressin use and adjunctive vasopressor burden showed numerical differences in treatment-effect estimates without significant interaction (**Supplementary Table S5, Figure S2**).

Centre-Level and Regional Heterogeneity

Within LMICs, treatment-effect estimates varied across institutional characteristics (**Supplementary Figure S3**). CRT-PHR was associated with a larger WR estimate in public centres ($n = 402$; WR 1.32, 95% CI 1.28–1.35) than in private centres ($n = 250$; WR 0.96, 95% CI 0.92–1.01), with suggestive treatment-by-ownership heterogeneity (interaction $p = 0.081$). Estimates also differed according to ICU size: WR 0.91 (95% CI 0.78–1.06) in ICUs with ≤ 15 beds, 1.34 (1.31–1.38) in those with 16–25 beds, and 0.92 (0.87–0.98) in ICUs with > 25 beds (interaction $p = 0.081$). University-affiliated centres had a WR of 1.21 (1.19–1.23) compared with 0.84 (0.74–0.96) in non-university centres, although formal interaction was not supported ($p = 0.348$).

Treatment-effect estimates also varied descriptively across LMIC countries, ranging from 1.90 (95% CI 1.39–2.59) in India and 1.28 (1.24–1.32) in Mexico to 1.15 (1.09–1.21) in Colombia and 0.85 (0.71–

1.03) in Argentina; estimates for Ecuador were imprecise because of the small sample, and Brazil was not displayed because of insufficient sample size (**Supplementary Figure S3**).

Regional treatment-effect estimates included a WR of 1.44 among patients enrolled in Latin American HICs (Chile and Uruguay) and 1.12 among those enrolled in Latin American LMICs (**Supplementary Figure S4**). Mortality also varied substantially according to institutional context within LMICs: approximately 35% in public centres compared with 20–23% in private centres, the latter approaching the overall HIC mortality of 24.6%.

DISCUSSION

In this post hoc analysis of ANDROMEDA-SHOCK-2, patients treated in LMIC centres were younger, had higher lactate levels, a greater prevalence of abnormal CRT, and substantially higher vasopressin use than those treated in HIC centres. Despite these differences, treatment-effect estimates for CRT-guided personalised hemodynamic resuscitation on the hierarchical primary outcome were similar across income groups, with WRs of 1.16 in LMICs and 1.18 in HICs and no evidence of treatment-effect modification by country income level. Within LMICs, baseline lactate showed the strongest patient-level exploratory signal of heterogeneity, with a WR of 1.57 among patients with lactate > 4 mmol/L versus 0.93 among those with lactate 2–4 mmol/L. Centre-level analyses further identified heterogeneity across institutional characteristics, particularly hospital ownership and ICU size.

Patients enrolled in LMIC centres had a distinct baseline profile, with younger age, lower APACHE II and slightly higher SOFA scores, higher lactate levels, more frequent abnormal CRT, and substantially greater baseline vasopressin use. A similar age–severity pattern was reported in MOSAICS-II, where patients from lower-income settings were younger and had lower overall illness severity than those from HICs. [4] Differences in clinical presentation have also been described within LMICs; in an Argentine multicentre cohort, patients treated in public hospitals were younger and had higher lactate, APACHE II, SOFA, and more frequent septic shock. [9] Against this clinical heterogeneity, treatment-effect estimates for CRT-PHR were similar across income groups, with WRs of 1.16 in LMICs and 1.18 in HICs and no evidence of treatment-effect modification by country income level. Given the recognised heterogeneity of treatment effects in septic shock, this consistency across income settings adds information beyond the average treatment effect reported in the parent trial. [20, 21] In ANDROMEDA-SHOCK-2, the hierarchical benefit was driven primarily by shorter duration of vital-organ support, without a significant reduction in mortality. [12] A similar treatment-arm mortality pattern was observed within LMICs at 28 and 90 days.

Baseline lactate showed the strongest exploratory signal of treatment-effect heterogeneity within LMICs. Patients with lactate > 4 mmol/L had a larger treatment-effect estimate (WR 1.57) than those with lactate 2–4 mmol/L (WR 0.93), with a treatment-by-lactate interaction $p = 0.002$. Prior studies have established lactate > 4 mmol/L as a marker of higher-risk septic shock and shown that lactate and peripheral perfusion may diverge during early resuscitation. [22, 23] Our results raises the possibility that baseline lactate may identify heterogeneity in response to CRT-PHR. Given the post hoc nature of the

analysis and multiplicity of subgroup testing, this finding remains hypothesis-generating and requires prospective validation. However, is an important consideration that critical care clinicians could make next to the bedside, knowing that these group of patients may benefit the most when using CRT-PHR as reanimation strategy.

Importantly, national income classification did not fully capture heterogeneity within LMIC settings. Treatment-effect estimates were larger in public than private hospitals (WR 1.32 vs 0.96; interaction $p = 0.081$) and differed across ICU-size categories, with the largest estimate observed in units with 16–25 beds (WR 1.34; interaction $p = 0.081$). University affiliation showed a similar numerical contrast, although without statistical evidence of interaction. Estimates also varied across individual LMIC countries and within Latin America, where HIC centres in Chile and Uruguay had a higher WR than Latin American LMIC centres. Mortality showed a parallel institutional gradient, approaching 35% in public LMIC hospitals compared with approximately 20–23% in private LMIC hospitals, the latter resembling mortality observed in HICs. Centre-level analyses were post hoc and based on unevenly represented strata, limiting inference on institutional effect modification.

Baseline vasopressin use was nearly twice as frequent in LMICs as in HICs (59.4% vs 29.5%), despite similar norepinephrine doses at randomisation (0.23 vs 0.20 $\mu\text{g/kg/min}$) and identical median pre-randomisation fluid administration (1500 mL in both groups). This dissociation suggests that vasopressin exposure at enrolment reflected differences in vasopressor escalation practice in addition to underlying shock physiology. International data support substantial variability in vasopressin prescription in septic patients. For instance, the PRESS survey showed wide variation in norepinephrine dose and duration thresholds used to introduce vasopressin, while Latin American data from the LIVEN network documented heterogeneity in resources and septic-shock management across regional ICUs. [24, 25] Within LMICs, CRT-PHR was associated with a numerically larger treatment-effect estimate among patients receiving vasopressin at baseline (WR 1.39 vs 1.12), although the treatment-by-vasopressin interaction was not significant and the pattern differed in HICs. Baseline vasopressin use may represent a marker of the prevailing hemodynamic treatment context, without evidence that it independently modified the effect of CRT-PHR.

This analysis has several strengths and limitations. It leveraged a large multinational randomised trial, preserved the original treatment allocation and intention-to-treat framework within income strata, and included 652 patients from six middle-income countries, representing settings often underrepresented in critical care trials. Country income group was not randomised and represents an ecological classification that does not directly capture ICU resources, healthcare access, organisational characteristics, or local resuscitation capacity. The additional centre-level analyses partly address this limitation by demonstrating substantial heterogeneity within LMIC settings, although these comparisons remain post hoc, are susceptible to unequal centre contribution and sparse strata, and should not be interpreted causally. Multiple subgroup analyses without multiplicity adjustment further increase the possibility of chance findings. Generalisability remains constrained by the parent trial eligibility criteria

and absence of low-income countries; findings should therefore be interpreted within the middle-income settings represented in ANDROMEDA-SHOCK-2.

In this post hoc analysis of ANDROMEDA-SHOCK-2, CRT-guided personalised haemodynamic resuscitation produced similar overall treatment-effect estimates in LMICs and HICs despite marked differences in baseline characteristics and resuscitation practice. Centre-level analyses showed that LMIC settings were themselves heterogeneous, with treatment-effect estimates varying according to hospital ownership, ICU size, and country, reinforcing the limitations of national income classification as a proxy for local critical-care context. Baseline lactate > 4 mmol/L remained the strongest patient-level exploratory signal of heterogeneity, whereas baseline vasopressin use did not significantly modify treatment effect. For clinicians treating septic shock where resources are scarce, the message is clear: the fingertip may reveal what the monitor cannot.

Declarations

Funding

This study was supported by Universidad de La Sabana (MED-357-2023), Chía, Colombia; Wellcome Trust (303666/Z/23/Z); UK International Development (301542-403); and the Gates Foundation (INV-063472).

Competing interests

The authors declare no competing interests relevant to this work.

Ethics approval

This study is a secondary analysis of the ANDROMEDA-SHOCK-2 randomized clinical trial. The parent trial was approved by the institutional review board or ethics committee at each participating site and was conducted in accordance with applicable local regulations and international ethical standards. No additional ethics approval was required.

Consent to participate

Written informed consent for participation in the parent trial was obtained from patients or their legally authorized representatives according to local regulations.

Data availability

The data supporting this analysis derive from the ANDROMEDA-SHOCK-2 trial. Deidentified participant data are available to researchers who submit a methodologically sound written proposal, subject to approval by a committee designated by the ANDROMEDA-SHOCK-2 Investigators. Data requests may be directed to glennnguru@gmail.com.

Authors' contributions

Conceptualization: Alex Julián Forero-Delgadillo, Natalia Sanabria-Herrera, Jeison Andrés Morales-Olivera, Luis Felipe Reyes; **Methodology:** Alex Julián Forero-Delgadillo, Natalia Sanabria-Herrera; **Formal**

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References

1. La Via L, Sangiorgio G, Stefani S et al (2024) The global burden of sepsis and septic shock. *Epidemiologia (Basel)* 5:456–478. <https://doi.org/10.3390/epidemiologia5030032>
2. Stephen AH, Montoya RL, Aluisio AR (2020) Sepsis and septic shock in low- and middle-income countries. *Surg Infect (Larchmt)* 21:571–578. <https://doi.org/10.1089/sur.2020.047>
3. Jawad I, Luksic I, Rafnsson SB (2012) Assessing available information on the burden of sepsis: global estimates of incidence, prevalence and mortality. *J Glob Health* 2:010404. <https://doi.org/10.7189/jogh.02.010404>
4. Li A, Ling L, Qin H et al (2022) Epidemiology, management, and outcomes of sepsis in ICUs among countries of differing national wealth across Asia. *Am J Respir Crit Care Med* 206:1107–1116. <https://doi.org/10.1164/rccm.202112-2743OC>
5. Chiu C, Legrand M (2021) Epidemiology of sepsis and septic shock. *Curr Opin Anaesthesiol* 34:71–76. <https://doi.org/10.1097/ACO.0000000000000958>
6. Tirupakuzhi Vijayaraghavan BK, Adhikari NKJ (2022) Sepsis epidemiology and outcomes in Asia: advancing the needle. *Am J Respir Crit Care Med* 206:1059–1060. <https://doi.org/10.1164/rccm.202207-1257ED>
7. Tancharoen L, Pairattanakorn P, Thamlikitkul V, Angkasekwinai N (2022) Epidemiology and burden of sepsis at Thailand's largest university-based national tertiary referral center during 2019. *Antibiot (Basel)* 11:899. <https://doi.org/10.3390/antibiotics11070899>
8. Azevedo LCP, Machado FR (2018) Sepsis in low- and middle-income countries. In: Wiersinga WJ, Seymour CW (eds) *Handbook of Sepsis*. Springer International Publishing, Cham, pp 231–251. https://doi.org/10.1007/978-3-319-73506-1_15
9. Estenssoro E, Loudet CI, Edul VSK et al (2019) Health inequities in the diagnosis and outcome of sepsis in Argentina: a prospective cohort study. *Crit Care* 23:250. <https://doi.org/10.1186/s13054-019-2522-6>
10. Almoosawy SA, Fernando SM, Rochweg B et al (2026) The association between socioeconomic position and mortality in patients with sepsis and septic shock—a systematic review and meta-analysis. *Crit Care Med* 54:692–700. <https://doi.org/10.1097/CCM.00000000000007053>

11. Hernandez G, Ospina-Tascon GA, Damiani LP et al (2019) Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: the ANDROMEDA-SHOCK randomized clinical trial. *JAMA* 321:654–664. <https://doi.org/10.1001/jama.2019.0071>
12. ; ANDROMEDA-SHOCK-2 Investigators for the ANDROMEDA Research Network, Spanish Society of Anesthesiology, Reanimation and Pain Therapy (SEDAR), Latin American Intensive Care Network (LIVEN), Hernandez G, Ospina-Tascón GA, Kattan E et al (2025) Personalized hemodynamic resuscitation targeting capillary refill time in early septic shock: the ANDROMEDA-SHOCK-2 randomized clinical trial. *JAMA* 334:1988–1999. <https://doi.org/10.1001/jama.2025.20402>
13. Castro R, Kattan E, Ferri G et al (2020) Effects of capillary refill time-vs. lactate-targeted fluid resuscitation on regional, microcirculatory and hypoxia-related perfusion parameters in septic shock: a randomized controlled trial. *Ann Intensive Care* 10:150. <https://doi.org/10.1186/s13613-020-00767-4>
14. Zampieri FG, Damiani LP, Bakker J et al (2020) Effects of a resuscitation strategy targeting peripheral perfusion status versus serum lactate levels among patients with septic shock: a Bayesian reanalysis of the ANDROMEDA-SHOCK trial. *Am J Respir Crit Care Med* 201:423–429. <https://doi.org/10.1164/rccm.201905-0968OC>
15. Hernandez G, Castro R, Bakker J (2020) Capillary refill time: the missing link between macrocirculation and microcirculation in septic shock? *J Thorac Dis* 12:1127–1129. <https://doi.org/10.21037/jtd.2019.12.102>
16. Hernandez G, Cavalcanti AB, Ospina-Tascon G et al (2018) Early goal-directed therapy using a physiological holistic view: the ANDROMEDA-SHOCK—a randomized controlled trial. *Ann Intensive Care* 8:52. <https://doi.org/10.1186/s13613-018-0398-2>
17. Kattan E, Bakker J, Estenssoro E et al (2022) Hemodynamic phenotype-based, capillary refill time-targeted resuscitation in early septic shock: the ANDROMEDA-SHOCK-2 Randomized Clinical Trial study protocol. *Rev Bras Ter Intensiva* 34:96–106. <https://doi.org/10.5935/0103-507X.20220004-en>
18. Orozco N, García-Gallardo G, Cavalcanti AB et al (2025) Statistical analysis plan for hemodynamic phenotype-based, capillary refill time-targeted resuscitation in early septic shock: the ANDROMEDA-SHOCK-2 randomized clinical trial. *Crit Care Sci* 37:e20250140. <https://doi.org/10.62675/2965-2774.20250140>
19. World Bank (n.d) World Bank Country and Lending Groups. <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>
20. Graham Linck EJ, Goligher EC, Semler MW, Churpek MM (2024) Toward precision in critical care research: methods for observational and interventional studies. *Crit Care Med* 52:1439–1450. <https://doi.org/10.1097/CCM.0000000000006371>
21. Spicer AB, Cavalcanti AB, Zampieri FG (2024) Subgroup analyses and heterogeneity of treatment effects in randomized trials: a primer for the clinician. *Curr Opin Crit Care* 30:427–438.

<https://doi.org/10.1097/MCC.0000000000001186>

22. Casserly B, Phillips GS, Schorr C et al (2015) Lactate measurements in sepsis-induced tissue hypoperfusion: results from the Surviving Sepsis Campaign database. Crit Care Med 43:567–573. <https://doi.org/10.1097/CCM.0000000000000742>

23. Kattan E, Hernandez G, Ospina-Tascon G et al (2020) A lactate-targeted resuscitation strategy may be associated with higher mortality in patients with septic shock and normal capillary refill time: a post hoc analysis of the ANDROMEDA-SHOCK study. Ann Intensive Care 10:114. <https://doi.org/10.1186/s13613-020-00732-1>

24. Jozwiak M, Cousin VL, De Backer D et al (2025) Vasopressin use across shock states: international insights from an international ESICM-endorsed survey: the PRESS Survey. Crit Care 29:273. <https://doi.org/10.1186/s13054-025-05505-5>

25. Castro R, Nin N, Ríos F et al (2018) The practice of intensive care in Latin America: a survey of academic intensivists. Crit Care 22:39. <https://doi.org/10.1186/s13054-018-1956-6>

Tables

Tables 1 and 2 are not available with this version.

Figures

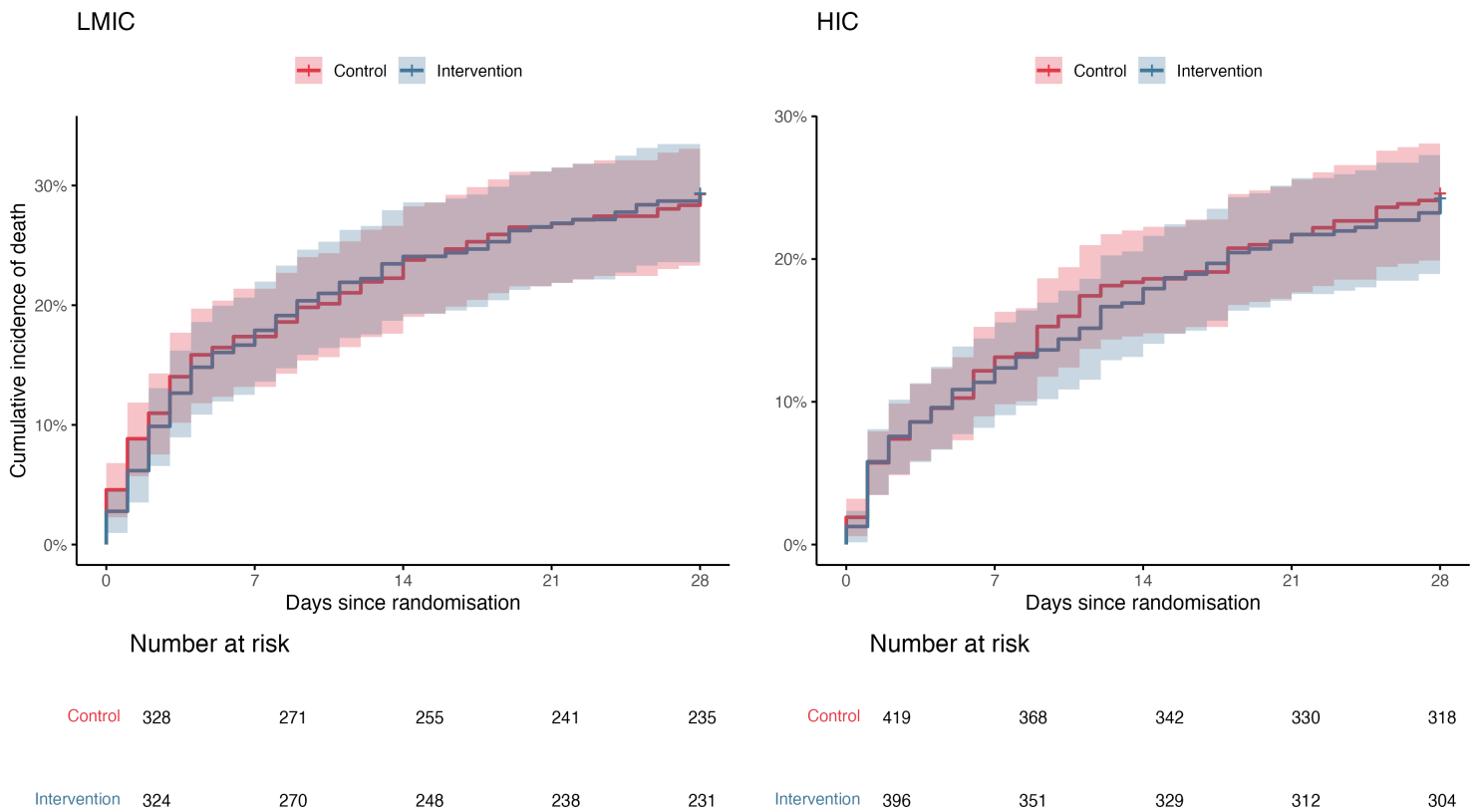


Figure 1

Cumulative Incidence of 28-Day All-Cause Mortality According to Treatment Allocation, Stratified by Country Income Level. Cumulative incidence curves (1 – Kaplan-Meier survival function) for the intervention (CRT-guided personalised hemodynamic resuscitation) and control arms, shown separately for low- and middle-income countries (LMIC, left panel) and high-income countries (HIC, right panel). Numbers at risk are shown below each panel at 0, 7, 14, 21, and 28 days. Shaded areas represent 95% confidence intervals. CRT, capillary refill time; HIC, high-income country; LMIC, low- and middle-income country.

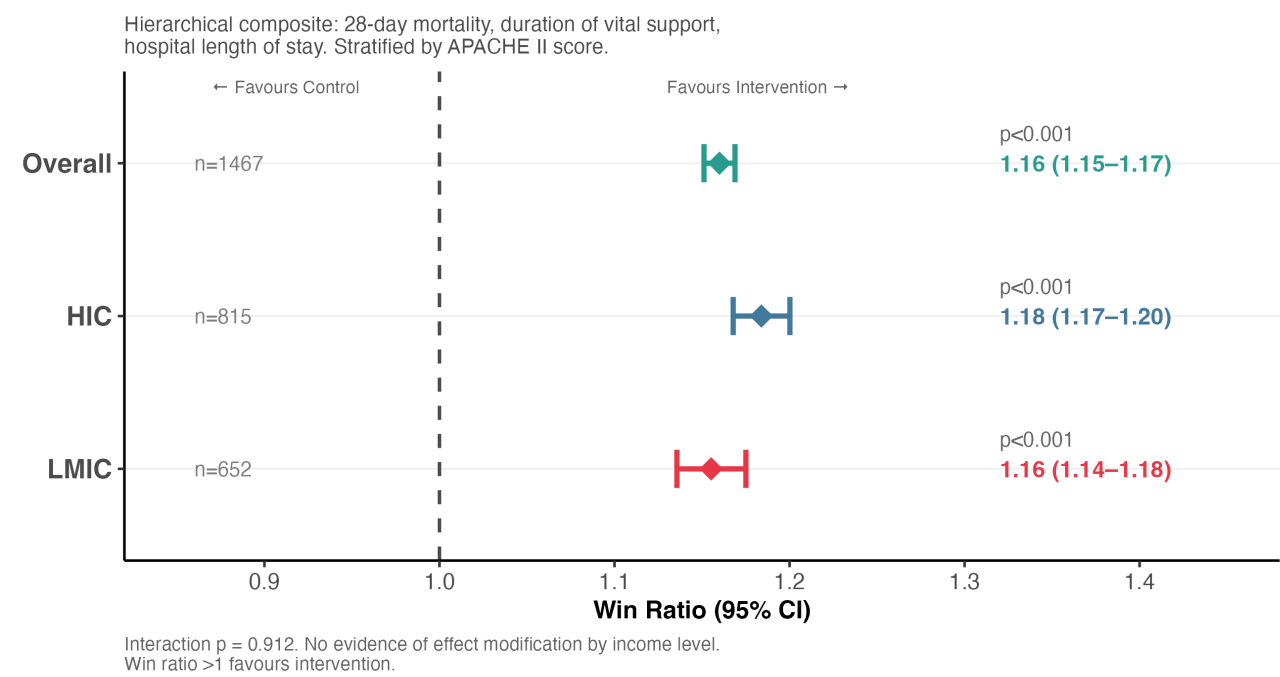
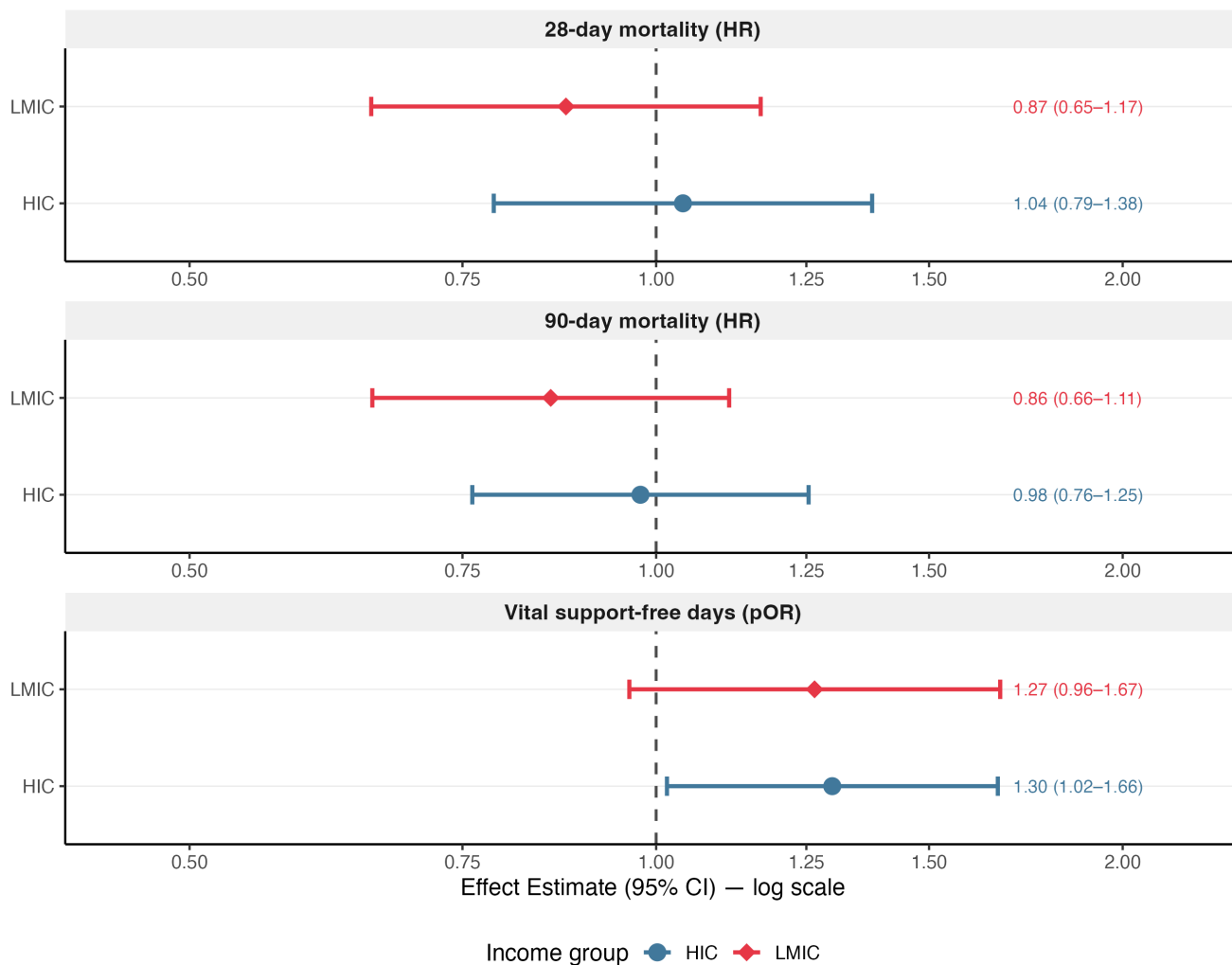


Figure 2

Win Ratio for the Hierarchical Composite Primary Outcome According to Country Income Level. Forest plot showing the stratified win ratio (95% confidence interval) for the hierarchical composite endpoint in the overall population, low- and middle-income countries (LMIC), and high-income countries (HIC). The win ratio was stratified by median APACHE II score (cut-point: 19). The hierarchical composite comprised: (1) 28-day all-cause mortality; (2) duration of vital organ support; (3) hospital length of stay truncated at 28 days. A win ratio >1 favours the CRT-guided intervention. The interaction p-value was derived from a likelihood ratio test of ordinal regression models with and without a treatment-by-income interaction term (p=0.912). Diamond symbols represent point estimates; horizontal lines represent 95% confidence intervals. Sample sizes (n) are shown to the left of each row. APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; CRT, capillary refill time.



HR <1 favours intervention for mortality outcomes.
pOR >1 favours intervention for vital support-free days.

Figure 3

Secondary Outcomes According to Country Income Level. Forest plot showing adjusted effect estimates for secondary outcomes in low- and middle-income countries (LMIC) and high-income countries (HIC). Hazard ratios (HRs) for 28-day and 90-day all-cause mortality were derived from Cox proportional hazards models adjusted for APACHE II score; HR < 1 favours the intervention. Proportional odds ratios (pOR) for vital support-free days were derived from ordinal logistic regression adjusted for APACHE II score; pOR >1 favours intervention. All models used the Efron method for ties. Horizontal lines represent 95% confidence intervals on a log scale. CI, confidence interval; HIC, high-income country; HR, hazard ratio; LMIC, low- and middle-income country; pOR, proportional odds ratio.

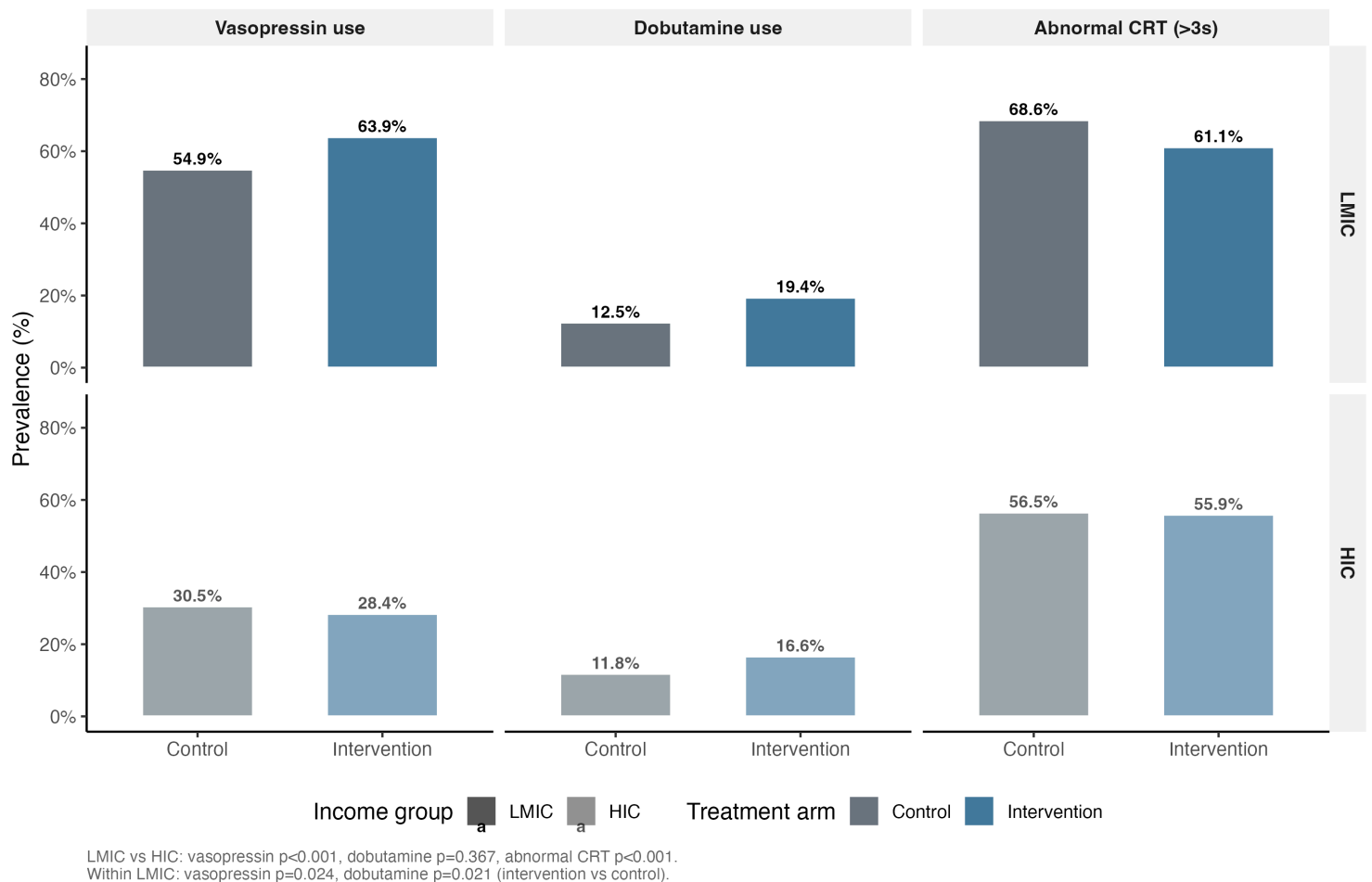


Figure 4

Resuscitation Patterns at Baseline According to Country Income Level and Treatment Allocation. Bar charts showing the prevalence of key resuscitation variables at the time of randomisation, stratified by income group (LMIC vs HIC) and treatment arm (Control vs Intervention). P-values for LMIC vs HIC comparisons (collapsing treatment arms): vasopressin $p < 0.001$, dobutamine $p = 0.367$, abnormal CRT $p < 0.001$. Within the LMIC subgroup, vasopressin use ($p = 0.024$) and dobutamine use ($p = 0.021$) were significantly higher in the intervention arm. CRT, capillary refill time; HIC, high-income country; LMIC, low- and middle-income country.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementary.docx](#)
- [AndromedaCollaborators.xlsx](#)
- [CONSORT2025editablechecklist.docx](#)
- [FigS1.SubgroupCRTLactate.png](#)
- [FigS2.VasopressorAnalysis.png](#)

- [FigS3.CentreHeterogeneity.png](#)
- [FigS4.RegionalHeterogeneity.png](#)