Research Square

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Urine Output and Hemodynamic Events After Loop-Diuretic Bolus During Low-Dose Norepinephrine: A Retrospective MIMIC- IV Cohort Study

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Research Article

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Abstract

Background

We characterized fluid and blood-pressure responses after recorded loop-diuretic bolus during low-dose norepinephrine.

Methods

Adults with an infection-associated shock proxy in MIMIC-IV were included at their first recorded loop-diuretic bolus 6 to < 72 hours after onset if norepinephrine was 0.005–0.2 micrograms/kg/min and preceding median MAP was > = 65 mm Hg. Prior postshock loop input or current renal replacement therapy excluded patients. The primary outcome was any hourly median MAP < 65 mm Hg within six hours. Post hoc analyses assessed urine output and net balance; eICU-CRD assessed external MAP ascertainment.

Results

Of 8,610 source patients, 270 met bolus criteria. Recorded urine output increased in 247/267 (92.5%; 95% CI 88.7–95.1%), with a median paired change of + 4.63 mL/kg; 172/268 (64.2%) had negative recorded net balance. A low-MAP hour occurred in 101/270 (37.4%; 31.9–43.3%), two adjacent low-MAP hours in 41/270 (15.2%), and norepinephrine escalation in 72/270 (26.7%). Older age (adjusted OR per SD 1.43, 95% CI 1.08–1.91) and lower prebolus MAP (OR per SD higher MAP 0.41, 0.29–0.58) were associated with low MAP in a post hoc model. In a broader 324-patient sensitivity cohort, 293/320 (91.6%) had increased urine output and 128/324 (39.5%) had low MAP. In eICU-CRD, 12/26 (46.2%) had low MAP after an order.

Conclusions

Increased recorded urine output and negative six-hour ICU balance were common after loop-diuretic bolus during low-dose norepinephrine. Lower prebolus MAP remained associated with subsequent low MAP in an exploratory adjusted model. Prebolus MAP may help prioritize circulatory monitoring during de-resuscitation.

Background

Fluid removal may begin while a patient with infection-associated shock still receives vasopressor support. The 2026 Surviving Sepsis Campaign guideline conditionally suggests active fluid removal after the acute resuscitation phase, while explicitly advising consideration of vasopressor dose, course, cardiorespiratory function, edema, weight, and fluid balance; the evidence certainty is very low [1].

Observational sepsis cohorts link higher positive fluid balance with mortality, although they cannot establish that removing fluid reverses this risk [2,3]. A conservative fluid protocol improved ventilator-free days in acute lung injury, whereas the CLASSIC and CLOVERS trials addressed restriction of further fluid administration in septic shock or sepsis-induced hypotension, not the immediate response to a diuretic bolus [4–6]. A systematic review found no established mortality benefit of active de-resuscitation in randomized septic-shock evidence [7]. The guideline does not specify an immediately safe norepinephrine dose or a short-term MAP response to the first loop-diuretic bolus.

The question is not wholly unstudied. Bandak and colleagues measured urine output and vasopressor requirements over six hours around diuretic administration during vasopressor support [8]. More recent cohorts examined active fluid de-escalation after hemodynamic stability, early versus late loop-diuretic initiation in sepsis, and loop timing in sepsis-associated acute kidney injury, mainly using later outcomes [9–11]. Diuretic responsiveness during de-resuscitation has also been studied in a broader ICU population [12]. An acute heart-failure study evaluated hypotension during the six hours after intravenous furosemide, but in a different clinical population [13]. The present analysis narrows the decision point to the first recorded postshock intravenous bolus during low-dose norepinephrine and directly describes index-anchored raw MAP observations. It is a descriptive study; a convincing untreated comparator was not established.

We aimed to describe the joint pattern of urine output, ICU-recorded net fluid balance, low-MAP events, and norepinephrine escalation around this decision, quantify observation coverage, and identify limitations that determine whether a subsequent comparative study is feasible.

Methods

Data source and design

We analyzed locally held MIMIC-IV v3.1 ICU and hospital records, including medication inputs, blood-pressure charting, fluid inputs and outputs, and derived infection and organ-dysfunction concepts [14,15]. This was a retrospective, single-center cohort. We selected the first qualifying shock ICU stay per adult patient.

The source phenotype combined an existing infection/organ-dysfunction concept, vasopressor exposure near the infection time, and lactate above 2 mmol/L within six hours before or after vasopressor initiation. We refer to this operational phenotype as an *infection-associated shock proxy* [16]. The source cohort contained 8,610 adults.

Index treatment and eligibility

Index time was the start time of the earliest recorded intravenous furosemide or bumetanide input during postshock hours 6 to < 72. We required an active norepinephrine record at 0.005–0.2

micrograms/kg/min, at least two preceding-two-hour MAP chart times, preceding-two-hour median MAP at least 65 mm Hg, no earlier recorded loop-diuretic input since shock onset or recent overlapping loop input, and no concurrent renal replacement therapy. Records with Rewritten or Paused status were excluded from the index selection. The primary cohort additionally required a missing infusion rate unit in the selected loop record, corresponding in this extract to a recorded medication bolus. Eligibility was based on information available at index time; future ICU residence and MAP coverage were evaluated as outcomes of data ascertainment, not entry criteria.

The 270 selected records were labeled FinishedRunning and 05-Med Bolus, with a median recorded duration of one minute; all selected amounts were positive and in milligrams. When a bolus and an infusion record shared the earliest start time, we selected the bolus. The selected event was the first recorded postshock loop-diuretic bolus. Same-time input and nearby eMAR details are reported in Supplementary Table S4.

Blood pressure and other measures

We extracted raw MAP chart events with item IDs 220052, 220181, and 225312, retaining plausible values of 35–140 mm Hg. At a shared timestamp, arterial values took precedence over noninvasive MAP; multiple values within the preferred modality were averaged. Six one-hour bins were anchored to index time, and the median available MAP within each bin was calculated. The main outcome was at least one observed hourly median below 65 mm Hg. Separate descriptive outcomes were any hourly median below 60 mm Hg and two *adjacent index-anchored hourly bins* with observed medians below 65 mm Hg. The 65-mm Hg threshold reflects a commonly studied septic-shock pressure target [17,18]. We tabulated the number of observed bins for each patient. Pre-index qualification used the local derived vital-sign table, whereas outcomes were calculated from raw chart events; arterial-only and coverage-restricted analyses assessed robustness to these measurement choices.

The norepinephrine endpoint required a new input record beginning 30 minutes to less than six hours after index, with a rate at least 25% above the active index rate and a recorded duration of at least 15 minutes. Cumulative fluid balance was computed from ICU-recorded inputs and outputs up to index and divided by recorded weight.

In a post hoc analysis, urine-output records were summed separately over [index − 6 hours, index) and [index, index + 6 hours), using the ICU urinary-output item IDs and subtracting genitourinary irrigant input. Each six-hour total was divided by the last available recorded weight at index; patients without records in either window were excluded from paired changes. Post-index ICU-recorded net balance was the sum of eligible volume inputs, prorated for infusions crossing the window boundary, minus recorded outputs over [index, index + 6 hours), divided by weight. We did not treat absent input or output records as zero.

Statistical analysis

We report events among all 270 eligible bolus recipients because each had at least three observed MAP bins and remained in the ICU for six hours. Proportions have descriptive Wilson 95% CIs. MAP, norepinephrine, urine-output, and net-balance outcomes are reported separately with their available denominators. Fluid-balance categories and the six-hour fluid-response outcomes are descriptive and were developed during exploration; no subgroup effect test is presented. A post hoc sensitivity cohort selected each patient's first qualifying bolus during the original 6-<72-hour window after at least 12 hours without a recorded loop input, retaining the low-dose norepinephrine and pre-index MAP criteria. This definition includes patients with earlier postshock loop exposure and is not the primary incident-bolus population. We organized reporting using STROBE and the RECORD extension for routinely collected health data [19,20]; the item-by-item reporting map is in Additional file 1.

For exploratory adjusted associations with any low-MAP hour, we fit a logistic model using age, index norepinephrine rate, preceding raw MAP, ICU-recorded cumulative fluid balance, preceding oxygen saturation, and preceding completed-hour SOFA score. Complete cases were used. A separate post hoc sensitivity model in the expanded 324-patient cohort included age, norepinephrine rate, preceding MAP, SOFA, invasive ventilation, earlier postshock loop exposure, and time from shock to index. Model coefficients and 200-bootstrap optimism-corrected discrimination are reported in the Supplementary Material.

An exploratory patient-unique 1:1 risk-set match assessed the feasibility of a future treatment comparison. Its selection, balance diagnostics, and endpoint estimates are reported only in Supplementary Table S5. The analyses were developed after data inspection; no prospective analysis plan was registered.

External validation in eICU-CRD

We used eICU-CRD v2.0 as an independent external dataset for six-hour low-MAP event ascertainment [21]. All downloaded files matched the release's supplied SHA-256 manifest. A *single-dose IV loop order* defined the eICU index, reflecting the medication-order structure of that database. We required a broad infection-coded diagnosis, lactate > 2 mmol/L within six hours of the first convertible positive norepinephrine record, an order 6 to < 72 hours after that record, a norepinephrine rate of 0.005–0.2 micrograms/kg/min charted within the preceding hour, no earlier postproxy loop order, and pre-index MAP stability. We calculated the same index-anchored hourly MAP threshold using eICU arterial and noninvasive records. Database-specific exposure and measurement definitions are detailed in Supplementary Table S6.

Results

Study population

Among 8,610 adults with the infection-associated shock proxy, 270 met all index criteria (Fig. 1; Supplementary Table S1). Included patients were distributed across MIMIC anchor-year groups 2008–2010 (n = 56), 2011–2013 (n = 51), 2014–2016 (n = 59), 2017–2019 (n = 76), and 2020–2022 (n = 28). Sequential stages retained 4,211 with an earliest recorded loop input during postshock hours 6 to < 72, 610 with active norepinephrine at 0.005–0.2 micrograms/kg/min, 492 without a prior/recent loop record or current renal replacement therapy, and 281 with the specified preceding MAP stability before the final bolus-record restriction. The final group comprised 268 furosemide and two bumetanide records. Median recorded furosemide amount was 20 mg (10th–90th percentile, 10–100 mg); the two bumetanide amounts had a median of 1.5 mg. All 270 remained in ICU through the six-hour observation window and had at least three raw-MAP hourly bins; 249 (92.2%) had all six bins observed.

Table 1

Baseline characteristics at the recorded-bolus index. Values are median (IQR), count/denominator (%), or median with availability as specified. The variable dictionary and time windows are in Supplementary Table S2.

Baseline characteristic at bolus index	Descriptive value
Age, years	67.0 (IQR 57.3–75.0)
Female sex	103/270 (38.1%)
Norepinephrine, micrograms/kg/min	0.080 (IQR 0.042–0.104)
Pre-index raw MAP, mm Hg	Median 74.0
Pre-index arterial MAP observed	223/270 (82.6%)
ICU cumulative recorded net balance, mL/kg	39.9 (IQR 17.8–76.4)
Lactate, mmol/L	Median 2.1; available 231/270
Creatinine, mg/dL	Median 1.4; available 269/270
Preceding six-hour urine output, mL/kg	Median 2.7; available 269/270
Preceding two-hour oxygen saturation, %	Median 97.5; available 268/270
Most recent completed-hour SOFA	Median 9.0; available 270/270

The ICU cumulative recorded net balance was positive in 248/270 (91.9%) and at least + 20 mL/kg in 195/270 (72.2%). Median time from ICU admission to proxy shock onset was 2.9 hours. Baseline lactate was available for 231/270, creatinine for 269/270, and preceding urine output for 269/270; detailed fluid-input availability and timing are in Supplementary Table S2.

Six-hour fluid and circulatory responses

Recorded urine output rose after the index bolus in 247/267 patients with paired six-hour records (92.5%); the median within-patient increase was 4.63 mL/kg (IQR 1.42–9.86). A negative ICU-recorded

net balance occurred in 172/268 (64.2%) during the following six hours. Over the same period, 101/270 patients (37.4%) had at least one hourly median MAP < 65 mm Hg, 41/270 (15.2%) had two adjacent low-MAP hours, and 72/270 (26.7%) had a recorded norepinephrine increase (Tables 2–4). These results show that a substantial short-term fluid response and circulatory events can coexist during low-dose norepinephrine support.

Table 2

Raw MAP observation and low-MAP event counts by index-anchored hour. Figure 2 displays these counts; an individual may contribute events in several hours.

Index-anchored hour after bolus	Patients with any raw MAP	Patients with arterial MAP	Patients with hourly median MAP < 65 mm Hg
0–<1	266	220	26
1–<2	266	220	34
2–<3	269	220	38
3–<4	261	216	33
4–<5	264	218	38
5–<6	267	220	45

Raw MAP was available in 1,593/1,620 possible patient-hours, and 249/270 (92.2%) had all six hourly bins observed. The hourly counts in Table 2 may include the same patient more than once (Fig. 2; Supplementary Table S3).

Table 3

Patient-level recorded events during the six hours after index. Percent intervals are Wilson 95% CIs.

Recorded event in the six hours after index	Events / eligible patients	Proportion (descriptive Wilson 95% CI)
Any observed hourly median MAP < 65 mm Hg	101/270	37.4% (31.9–43.3%)
Any observed hourly median MAP < 60 mm Hg	37/270	13.7% (10.1–18.3%)
Two adjacent observed hourly medians < 65 mm Hg	41/270	15.2% (11.4–20.0%)
Recorded norepinephrine increase > = 25% for > = 15 minutes, beginning 30 minutes to < 6 hours after index	72/270	26.7% (21.7–32.2%)

Table 4

Post hoc six-hour urine output and ICU-recorded fluid balance. Urine-output change compares each patient's six hours before and after index; net balance uses recorded post-index volume inputs minus outputs. Percent intervals are descriptive Wilson 95% CIs.

Recorded measure	Result	Available records
Pre-index urine output, median mL/kg	2.74	269/270 with a record
Post-index urine output, median mL/kg	8.22	268/270 with a record
Within-patient urine-output change, median (IQR) mL/kg	+ 4.63 (+ 1.42 to + 9.86)	267/270 with both windows
Higher urine output after index	247/267 (92.5%; 88.7–95.1%)	267/270 paired windows
Post-index net balance, median (IQR) mL/kg	-2.24 (-7.85 to + 2.65)	268/270 with recorded input and output
Negative post-index net balance	172/268 (64.2%; 58.3–69.7%)	268/270 with input and output

Median urine output increased from 2.74 mL/kg before index to 8.22 mL/kg afterward, and the median post-index recorded net balance was − 2.24 mL/kg (IQR − 7.85 to + 2.65). The median number of urinary-output records was six in both windows. Supplementary Table S7 gives source-item details and the exploratory composite combining urine output, net balance, MAP, and norepinephrine change.

The proportion with a low-MAP hour was similar after restricting to patients with complete six-hour MAP coverage (93/249, 37.3%). Excluding two patients with same-time bolus and drip records yielded 101/268 (37.7%) with low MAP and 70/268 (26.1%) with norepinephrine escalation (Supplementary Tables S3 and S4). Event counts by pre-index recorded balance are shown in Supplementary Table S7.

In a sensitivity analysis restricted to 220 patients with at least two preceding arterial MAP observations and median MAP > = 65 mm Hg, 82/220 (37.3%) had a subsequent low-MAP hour and 59/220 (26.8%) had recorded norepinephrine escalation (Supplementary Table S4).

The post hoc six-variable model included 268 patients and 100 low-MAP events. Older age was associated with higher odds of low MAP (adjusted OR per one SD 1.43, 95% CI 1.08–1.91), whereas higher pre-index MAP was associated with lower odds (adjusted OR per one SD 0.41, 0.29–0.58). Complete model coefficients are in Supplementary Table S5.

The broader first-eligible-bolus sensitivity definition yielded 324 patients, including 54 with earlier postshock loop exposure. Recorded urine output rose in 293/320 (91.6%) with paired records, 208/322 (64.6%) had negative post-index net balance, and low MAP occurred in 128/324 (39.5%). Two adjacent low-MAP hours occurred in 53/324 (16.4%), and norepinephrine escalation in 89/324 (27.5%). In a separate post hoc model for these 324 patients, older age (adjusted OR per 10 years 1.27, 95% CI 1.05–

1.52) and higher prebolus MAP (OR per 10 mm Hg 0.25, 0.16–0.39) showed associations in the same directions (Supplementary Table S7).

The post hoc matched comparison and its balance diagnostics are reported in Supplementary Table S5. Because the matched groups retained baseline imbalance, it was not used to estimate a treatment effect.

eICU external validation results

In eICU-CRD, 26 patients from seven hospitals met the order-based eligibility criteria; 25 had all six subsequent MAP hours observed. Twelve of 26 had an hourly median MAP < 65 mm Hg (46.2%; 95% CI 28.8–64.5%). Among 16 orders entered no later than their planned start, six patients had low MAP (37.5%). The second database reproduced ascertainment of the six-hour low-MAP event under an order-based index; the source and timing checks are detailed in Supplementary Table S6.

Discussion

The principal finding was a substantial short-term fluid response during continued low-dose norepinephrine support: 92.5% of patients with paired records had greater urine output, and 64.2% had negative ICU-recorded net balance over six hours. Low-MAP and norepinephrine-escalation events also occurred during this interval. Older age and lower prebolus MAP were associated with subsequent low MAP after adjustment, with associations in the same directions in the broader 324-patient sensitivity cohort. Together, these results show that early fluid removal and circulatory vulnerability can coexist at this decision point; a stable prebolus MAP alone does not capture the full subsequent response.

The 2026 guideline suggests considering active fluid removal after acute resuscitation but does not provide a short-term response profile for patients still receiving norepinephrine [1]. Bandak and colleagues studied six-hour urine-output and vasopressor trajectories during diuretic treatment [8], while more recent cohorts assessed de-escalation timing, loop initiation, and longer-term outcomes [9–12]. Our study focuses on an index-anchored first recorded bolus during low-dose norepinephrine and pairs the six-hour urinary response with granular MAP ascertainment. The similar event proportions under arterial-only monitoring and the broader eligibility definition support the consistency of this observed pattern. The eICU analysis further demonstrates that the low-MAP outcome can be measured in an independent database. The guideline's initial MAP range of 60–65 mm Hg for adults aged 65 years or older also supports interpreting single-hour < 65 events alongside the reported < 60 and adjacent-hour measures [1].

This study has several strengths. First, the first recorded postshock loop-diuretic bolus provides a clear clinical time anchor during low-dose norepinephrine support. Second, paired urine output and net balance were assessed alongside hourly MAP and norepinephrine changes, capturing the fluid and circulatory responses at the same decision point. Third, MAP coverage was high (1,593 of 1,620 possible patient-hours), and arterial-only, complete-coverage, and broader-eligibility analyses supported the

consistency of the low-MAP pattern. Finally, the independent eICU cohort confirmed that the six-hour low-MAP outcome can be ascertained in another critical care database. Together, these features provide a detailed short-term response profile for a common de-resuscitation decision.

Several limitations warrant consideration. The retrospective design, operational shock definition, and clinician-directed treatment leave room for residual confounding. ICU documentation may not capture all earlier fluid care or the precise timing of bedside administration and blood pressure measurement. The eICU analysis included 26 order-indexed patients and therefore supports external outcome ascertainment, rather than independent replication of the MIMIC bolus-specific associations. These limitations affect causal interpretation and generalizability; prospective multicenter studies with administration-level data should test whether joint fluid and circulatory assessment can improve treatment decisions and patient outcomes.

Conclusions

Among selected patients receiving low-dose norepinephrine after infection-associated shock, recorded urine output increased in 92.5% and six-hour ICU-recorded balance was negative in 64.2% after the first postshock loop-diuretic bolus. An observed low-MAP hour occurred in 37.4% despite prebolus MAP stability. Older age and lower prebolus MAP remained associated with subsequent low MAP after adjustment, with similar directions in the broader eligibility analysis. These findings support assessment of fluid and circulatory responses together during early de-resuscitation. The eICU cohort provided external confirmation that the six-hour low-MAP outcome could be ascertained in a second database.

Abbreviations

CI
confidence interval
eICU-CRD
eICU Collaborative Research Database
ICU
intensive care unit
MAP
mean arterial pressure
MIMIC-IV
Medical Information Mart for Intensive Care IV
OR
odds ratio
SD
standard deviation
SOFA
Sequential Organ Failure Assessment.

Declarations

Ethics approval and consent to participate:

Ethics approval and consent to participate: MIMIC-IV and eICU-CRD are deidentified databases accessed by a credentialed investigator under PhysioNet data use agreements. The MIMIC project was approved by the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center, with a waiver of individual informed consent for the use of deidentified data. The Independent Ethics Committee at The First People's Hospital of Kunshan approved this retrospective secondary analysis (approval No. 2025-03-014-H00-K01).

Competing interests:

The authors declare no potential conflicts of interest with respect to this research, authorship, or publication.

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Author Contribution

Tingting Yu: Conceptualization, Methodology, Software, Formal analysis, Data curation, Visualization, and Writing - original draft. Fang Jin: Investigation, Validation, Resources, and Writing - review and editing. Zhixiang Cai: Methodology, Validation, Funding acquisition, and Writing - review and editing. Yuan Peng: Conceptualization, Supervision, Project administration, and Writing - review and editing. Fuliang Cai: Conceptualization, Supervision, Project administration, and Writing - review and editing. All authors read and approved the final manuscript..

Data Availability

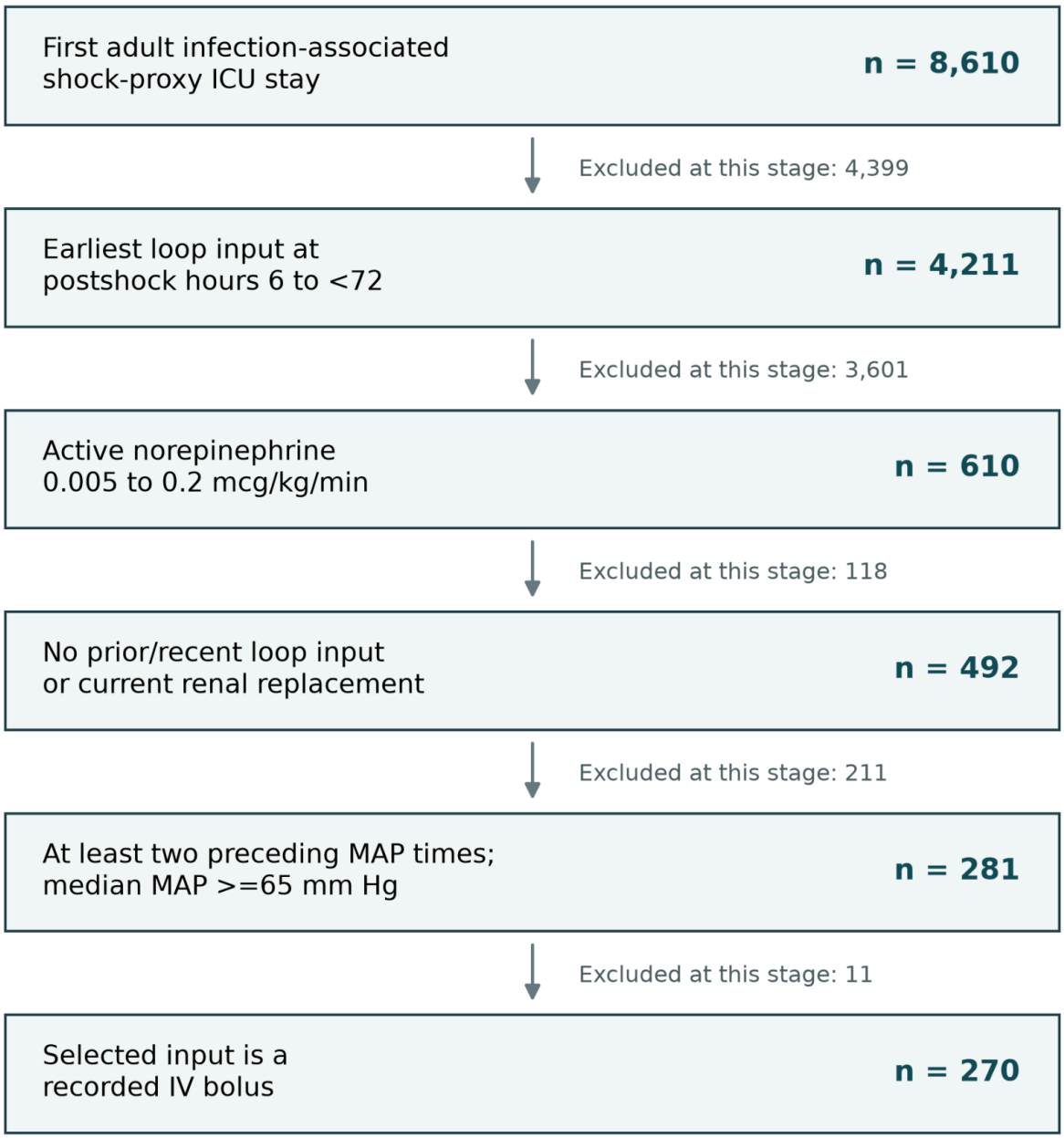
The datasets analyzed during the current study are publicly available in the MIMIC-IV database (https://physionet.org/content/mimiciv/) and the eICU Collaborative Research Database (https://physionet.org/content/eicu-crd/), accessible upon completion of the required training and data use agreement through PhysioNet.

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Figures



Sequential patient counts. Index treatment is a recorded input, not independently verified administration.

Figure 1

Sequential selection of the recorded-bolus cohort. Counts are patient counts after each sequential eligibility rule. The source phenotype is an infection-associated shock proxy, and the final stage specifies a recorded IV bolus.

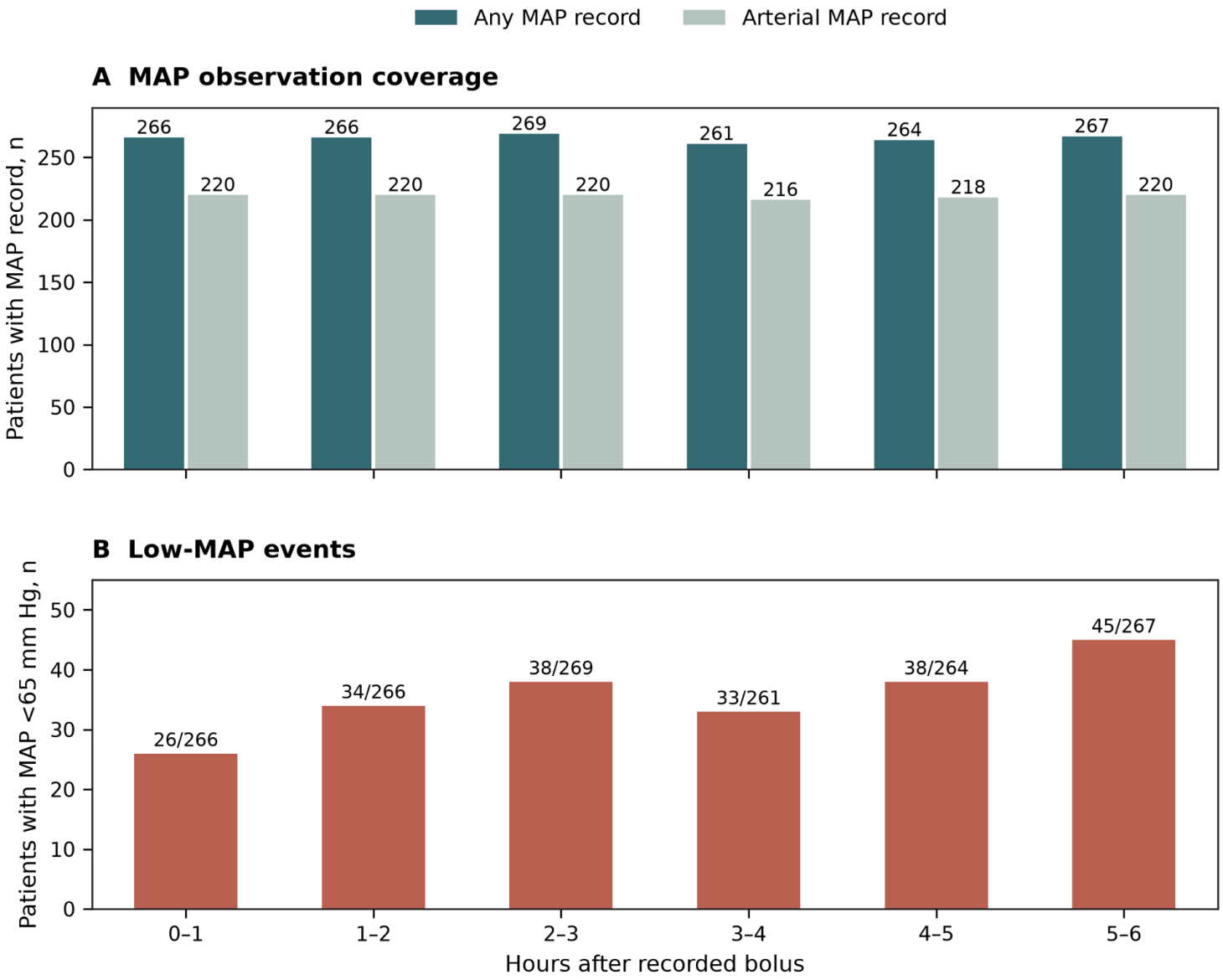


Figure 2

MAP ascertainment and recorded low-MAP events by index-anchored hour. Panel A shows the number of patients with any MAP record and with an arterial MAP record. Panel B shows patients whose observed hourly median MAP was <65 mm Hg; labels give events over patients with an observed MAP in that hour. Time intervals are left-closed and right-open. The cohort denominator is 270, and the same patient can contribute events to multiple hours.

Supplementary Files

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

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