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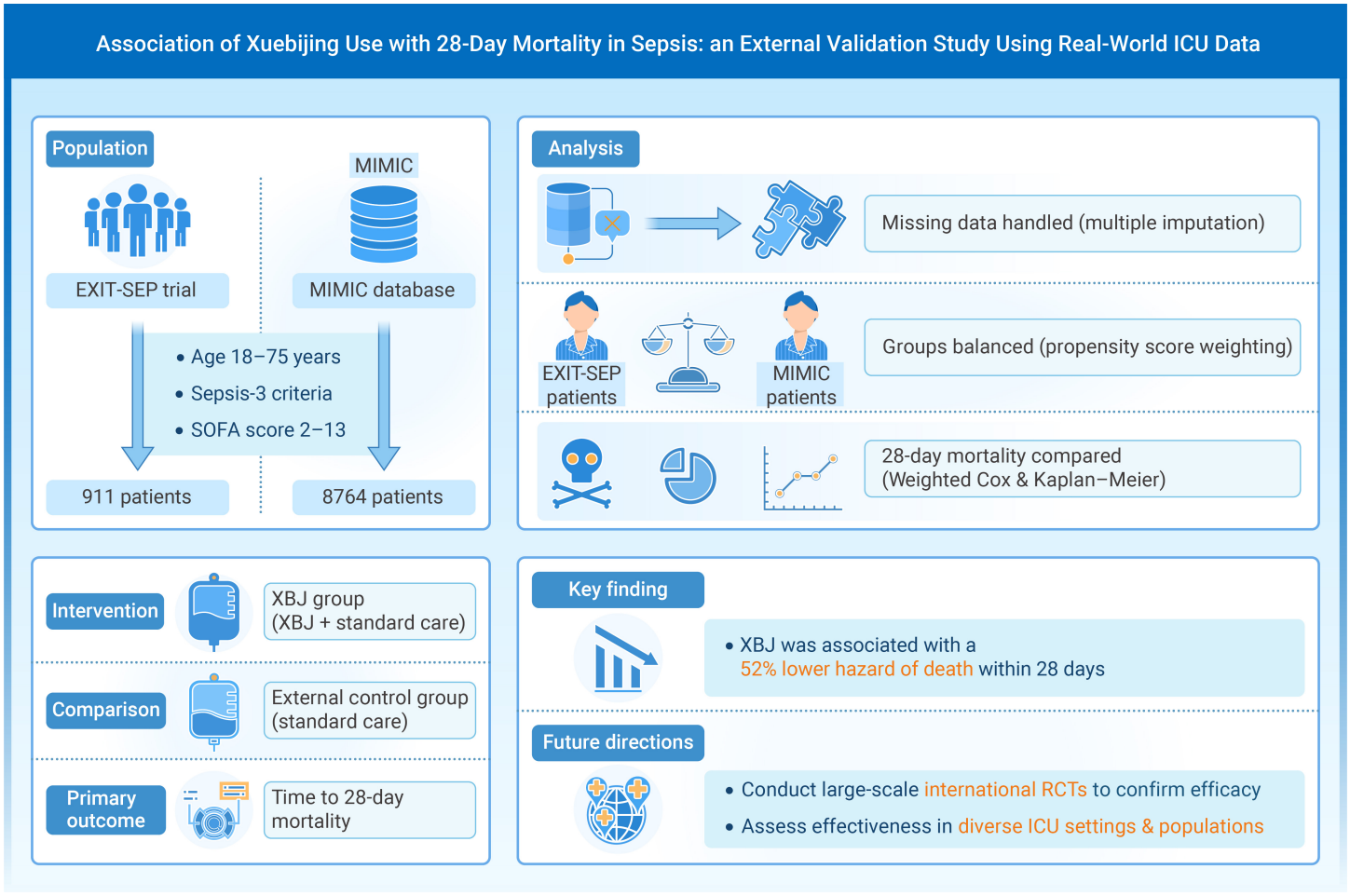
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Sepsis is a life-threatening condition with few proven drug treatments worldwide.
- Xuebijing injection (XBJ), a Chinese herbal medicine, showed benefits for sepsis patients in Chinese trials.
- We performed an external validation using U.S. ICU data (Medical Information Mart for Intensive Care IV, MIMIC-IV).
- Compared to the MIMIC-IV cohort, trial emulation showed XBJ lowered 28-day death risk (HR 0.48).

REPORT

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Background:Most pharmacologic interventions for sepsis have failed to show survival benefits in randomized trials. Xuebijing injection (XBJ), an approved intravenous drug widely used in China for sepsis, reduced mortality in two large randomized trials. However, its generalizability to non-Chinese populations remains uncertain. Our study aimed to assess the potential generalizability of the survival benefit of XBJ, previously observed in a Chinese randomized trial, to a non-Chinese ICU population and evaluated whether the treatment effect size was consistent across these different clinical settings. Methods:We conducted a retrospective comparative effectiveness study, conceptualized as a single-arm trial of XBJ with an external control cohort from the MIMIC-IV database, designed using trial emulation principles aligned with the EXIT-SEP trial. Patients with Sepsis-3 septic shock were included. The primary outcome was time to 28-day all-cause mortality. Propensity scores were estimated with generalized boosted models, overlap weighting was applied, and missing data were handled with multiple imputation. Secondary outcomes included ICU-free days, ventilator-free days, and hospital length of stay. Results:Among 911 patients treated with XBJ and 8,764 controls, unadjusted 28-day mortality rates were 18.1% and 15.5%, respectively. In the primary overlap-weighted analysis, XBJ was associated with a significantly reduced risk of 28-day mortality compared with external controls (HR, 0.48; 95% CI, 0.31–0.73). Findings were consistent across sensitivity analyses. ICU and hospital stays were longer among XBJ-treated patients (ICU: 10.3 vs 6.7; difference, 3.7 days [95% CI, 2.6–4.7]; hospital: 16.2 vs 12.4; difference, 4.0 days [95% CI, 2.6–5.4]). Conclusions:In this external validation using real-world ICU data, XBJ use was associated with reduced 28-day mortality among patients with sepsis. These findings support its potential generalizability beyond the original trial population but warrant confirmation in prospective studies across diverse settings.

INTRODUCTION

Sepsis remains a major cause of mortality in intensive care units (ICU) worldwide, despite advances in supportive care.[1] Numerous randomized clinical trials evaluating pharmacologic interventions, including immunomodulatory, anti-inflammatory, and anticoagulant therapies, have largely failed to demonstrate consistent mortality benefits.[2,3] This persistent absence of effective therapies underscores the need to explore complementary strategies and reassess promising signals from prior trials.

Xuebijing injection (XBJ), a standardized five-herb intravenous formulation, has been approved and widely used in China as an adjunctive therapy for sepsis. Mechanistic studies suggest that XBJ improves endothelial function and exerts anti-inflammatory, organ-protective effects.[4] Two large Chinese randomized controlled trials (RCTs), XBJ-SCAP and EXIT-SEP,[5,6] reported significant mortality reductions. EXIT-SEP showed a 7.3% absolute reduction in 28-day mortality compared with placebo. However, both trials were conducted exclusively in Chinese hospital settings, raising concerns about the generalizability of the findings.[7]

To evaluate whether the survival benefits extend to other populations, we conducted an external validation study[8] using the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, a large publicly available US critical care dataset. By applying trial-aligned eligibility criteria, we constructed an external control cohort and compared outcomes with XBJ-treated patients from the original trial.

MATERIALS AND METHODS

Study design and data sources

This was a retrospective comparative effectiveness study, conceptualized as a single-arm trial of XBJ with an external control cohort constructed from the MIMIC-IV database, using trial emulation principles aligned with the EXIT-SEP randomized clinical trial. Individual-level data of 911 patients treated with XBJ in EXIT-SEP were compared with an external control cohort drawn from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database (2008–2019). In EXIT-SEP, follow-up began at randomization. In our emulation, follow-up ("time zero") began when a patient first met all EXIT-SEP eligibility criteria during the ICU admission window. At this point, patients could in principle have been assigned to either XBJ or control. To mirror the EXIT-SEP protocol, we allowed a 24-hour grace period for treatment initiation.

Eligibility criteria and cohort construction

EXIT-SEP included patients aged 18 to 75 years, diagnosed with sepsis per Sepsis-3 criteria, and had a Sequential Organ Failure Assessment (SOFA) score between 2 and 13. Key exclusion criteria included: (1) sepsis onset >48 hours prior; (2) severe comorbidities (malignancies, hematologic diseases, HIV); (3) a liver or renal SOFA score ≥3; (4) organ transplantation or immunosuppressive therapy within 6 months; and (5) pregnancy or breastfeeding.

MIMIC-IV patients met the same criteria. Comorbidities were identified via ICD codes, and lab thresholds defined organ dysfunction (bilirubin ≥6 mg/dL, creatinine ≥3.5 mg/dL). Baseline comparability of EXIT-SEP and MIMIC-IV cohorts was assessed using Pocock criteria to approximate the standard-of-care environment of EXIT-SEP. Details on data harmonization, eligibility alignment, and trial-aligned treatment protocols are provided in Content S1. This study was designed and reported in line with the TARGET guideline for transparent reporting of observational studies emulating a target trial.[9]

Outcomes

The primary outcome was time to 28-day all-cause mortality. Secondary outcomes included lengths of ICU and hospital stay.

Statistical analysis

Patients who did not experience a primary endpoint event were censored at the time of hospital discharge. Cox proportional hazards regression models were used to estimate the association between XBJ administration and mortality, with initial models adjusting for demographic characteristics, clinical factors, and concomitant medications.

Given the nonrandomized nature of XBJ administration, propensity score methods were employed to reduce potential confounding. Individual propensity scores for XBJ receipt were estimated using a generalized boosted model (GBM) that included the same covariates as the multivariable Cox

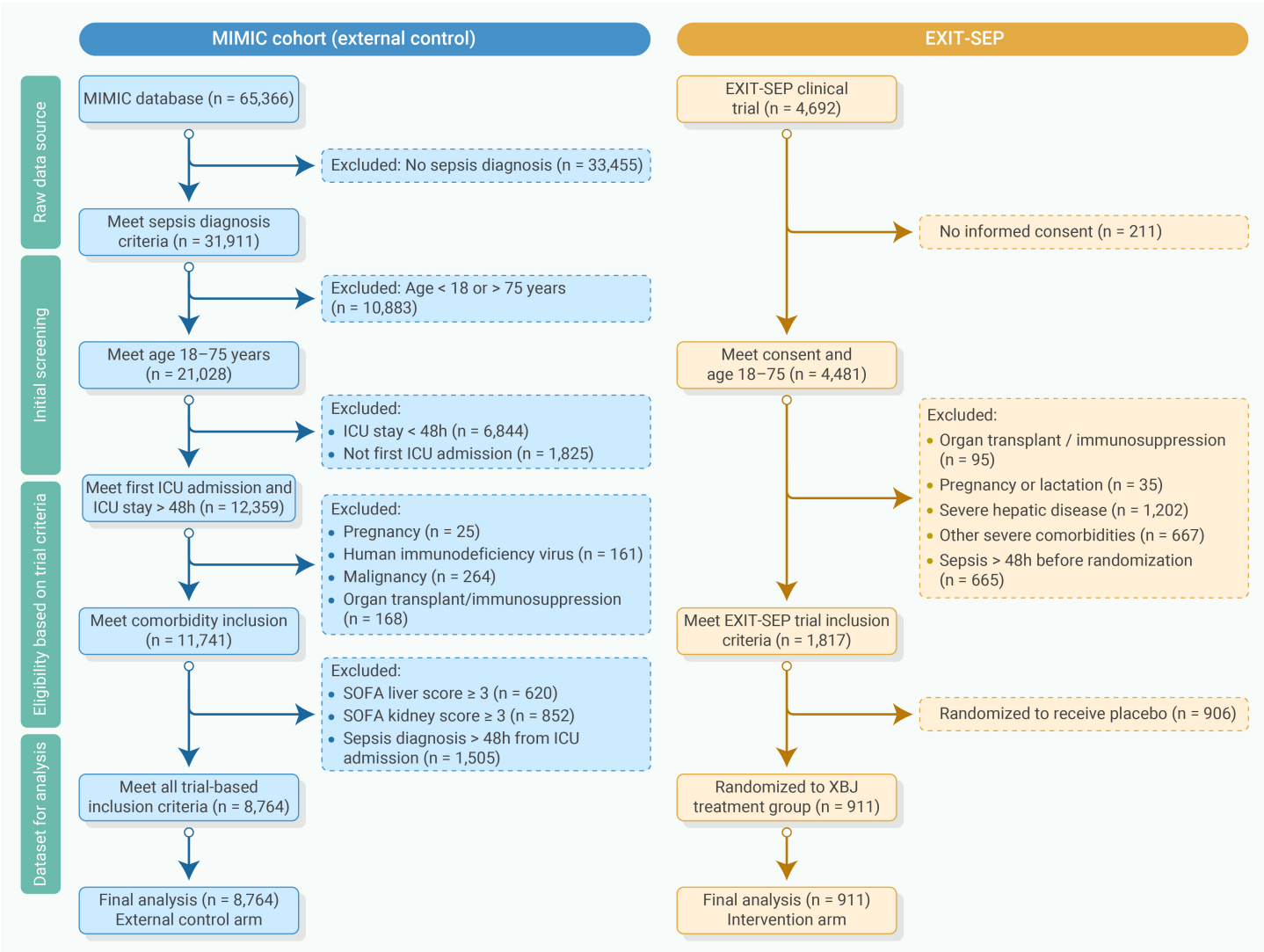


Figure 1. Study flow diagram.

model. The association between XBJ use and mortality was assessed through multivariable Cox regression models incorporating four propensity score approaches.

The primary analysis applied overlap weighting, using predicted probabilities from the propensity score model to calculate the overlap weights. Kaplan–Meier survival curves were constructed, and a weighted Cox proportional hazards model incorporating the overlap weights was fitted to estimate the association between treatment group (XBJ vs external control) and time-to-event outcomes. Secondary analyses included inverse probability weighting, in which stabilized weights were calculated from the propensity scores; covariate adjustment by including the propensity score as an additional covariate in the Cox model; and propensity score matching using a 1:1 nearest-neighbor matching algorithm with a caliper width of 0.2 of the standard deviation of the logit of the propensity score to create a matched sample.

Secondary continuous outcomes, including hospital length of stay, and ICU length of stay, were analyzed using survey-weighted linear regression models with overlap weighting, adjusting for the same covariates included in the propensity score model.

Multiple imputation was performed to address missing data, with the final analytic dataset selected based on the imputation model yielding the lowest Bayesian Information Criterion (BIC), following the approach proposed by Noghrehchi et al.[10] The nonparametric bootstrap method was used to obtain 95% pointwise confidence intervals for the overlap-weighted Kaplan–Meier curves. E-values for the primary hazard ratio and for the 95% confidence interval bound closest to the null were calculated to assess how strong an unmeasured confounder would need to be to explain away the observed association, using the approach described by VanderWeele and Ding.[11]

All statistical analyses were conducted using R software, version 4.4.3 (R Foundation for Statistical Computing). Detailed specifications of the multiple imputation procedures, propensity score estimation, weighting algorithms, and survival curve construction are provided in the Content S2.

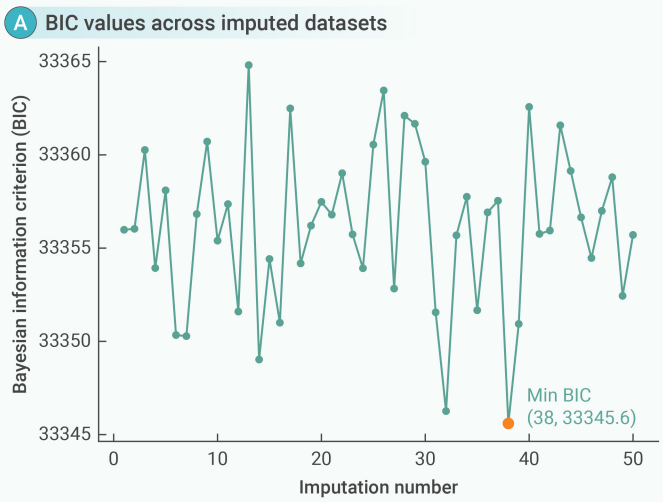
RESULTS

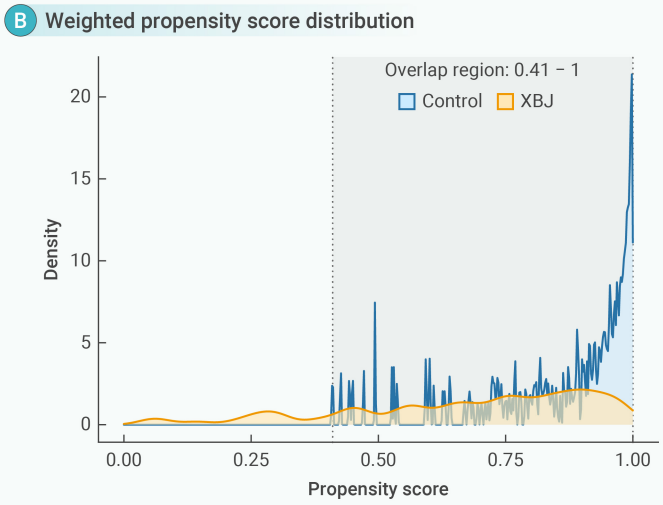
Cohort selection and imputation

A total of 9,675 patients were included in the analysis, comprising 911 patients who received XBJ in the EXIT-SEP trial and 8,764 external controls identified from MIMIC-IV after applying trial-aligned eligibility criteria (Figure 1). Among 50 multiply imputed datasets, the analytic dataset corresponding to the lowest Bayesian Information Criterion (BIC = 33,345.6 at imputation 38) was selected for the final analysis (Figure 2A). After applying overlap weighting, 99.9% of patients fell within the common support region of propensity scores (0.41–1), indicating substantial comparability between the XBJ and external control groups.

Propensity score distribution and covariate balance

Before weighting, baseline characteristics differed substantially between the two cohorts (Table 1). For example, XBJ-treated patients were more likely to be admitted to general ICUs, had higher SOFA scores, and exhibited greater prevalence of respiratory dysfunction, whereas external controls more often





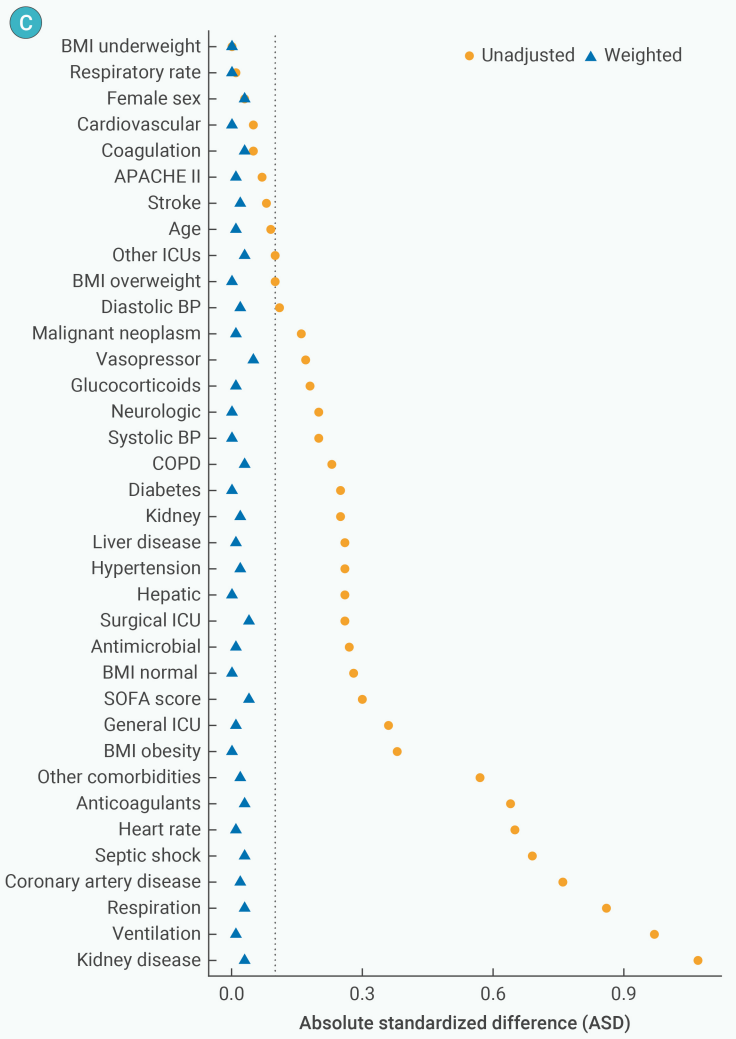


Figure 2. Imputation dataset selection and covariate balance assessment (A) Bayesian information criterion (BIC) values across imputed datasets. BIC values across 50 multiply imputed datasets; the dataset with the lowest BIC was selected for analysis. (B) Overlap-weighted propensity score distributions for patients receiving XBJ and external controls, showing substantial overlap after weighting. (C) Absolute standardized differences of baseline covariates before and after overlap weighting, demonstrating adequate covariate balance.

had chronic comorbidities such as hypertension, coronary artery disease, and chronic kidney disease. After overlap weighting, covariate balance was achieved across all measured variables, with standardized differences less than 0.1 (Figures 2B-C).

Primary and secondary outcomes

In the crude analysis, 28-day mortality was 18.1% (165/911) in the XBJ group and 15.5% (1,358/8,764) in controls (HR, 0.84; 95% CI, 0.71–0.99). After adjustment for all baseline covariates, the multivariable Cox model yielded an HR of 0.52 (95% CI, 0.41–0.66). In the primary analysis using overlap weighting, XBJ use was associated with a significantly lower risk of 28-day mortality (HR, 0.48; 95% CI, 0.31–0.73). Kaplan–Meier curves further illustrated the improved 28-day survival in the XBJ group (Figure 3). Findings were consistent across all sensitivity analyses (IPW: HR, 0.45; adjustment: HR, 0.50; matching: HR, 0.46 in Table 2). Associations between all baseline covariates and mortality are also shown in Table S4. In the propensity score–matched cohort (1:1 nearest-neighbor matching), baseline characteristics were well balanced, and XBJ treatment remained associated with improved 28-day survival (Table S5). The consistency of these findings with the primary overlap-weighted analysis supports the robustness of the observed treatment effect. An E-value analysis yielded an E-value of 3.59 for the point estimate (HR, 0.48) and 2.08 for the upper 95% CI limit (0.73), suggesting that only a strong unmeasured confounder could plausibly account for the observed survival benefit.

Secondary analyses showed longer ICU and hospital stays for the XBJ group. ICU stay: 10.3 vs 6.7 days (difference, 3.7; 95% CI, 2.6–4.7). Hospital stays: 16.2 vs 12.4 days (difference, 4.0; 95% CI, 2.6–5.4) (Table 3). Adverse events occurred in 22.9% of patients in the XBJ group with no unexpected safety signals observed (Table S7).

DISCUSSION

In this study, we conducted an external validation using a large U.S. ICU database and observed that XBJ was associated with a clinically meaningful reduction in 28-day mortality among patients with septic shock. The survival benefit was consistent across multiple analytic approaches. Secondary outcomes, such as ICU-free and ventilator-free days, also favored XBJ without evidence of increased harm. These findings provide external validation of the mortality reduction signal initially observed in Chinese randomized trials, thereby supporting the robustness of the observed treatment effect.

When compared with prior evidence, our results are consistent with two pivotal RCTs, EXIT-SEP in sepsis and XBJ-SCAP in severe pneumonia, both of which reported significant survival benefits with XBJ.[5,6] This external validation across diverse populations contrasts with the disappointing trajectory of most pharmacologic interventions for sepsis over the past decade, such as acetaminophen,[12] immunoglobulins,[13] β-d-Glucan[14] or vitamin C,[15] which failed to show consistent survival benefits. The consistency of XBJ's effect

Table 1. Characteristics of patients receiving or not receiving XBJ, before and after propensity score overlap weighting.[a]

Variable	Unadjusted			After overlap weighting		
	External control (n = 8,764)	XBJ (n = 911)	ASD	External control (n = 8,764)	XBJ (n = 911)	ASD
Demographic characteristics						
Age, mean (SD), y	57.6 (13.4)	56.31 (13.4)	0.09	55.8 (13.7)	55.7 (13.8)	0.01
Female Sex, %	39.7	36.3	0.03	42.4	39.8	0.03
BMI classification, %[b]						
Underweight	1.6	2.3	<0.001	2.7	2.7	<0.001
Normal	16.5	50.5	0.28	45.6	46.0	<0.001
Overweight	21.8	40.0	0.10	37.0	36.7	<0.001
Obesity	32.8	7.2	0.38	14.7	14.7	<0.001
Preadmission health						
ICU types, %						
General ICU	39.2	75.6	0.36	70.2	71.2	0.01
Surgical ICU	27.9	1.9	0.26	8.9	5.3	0.04
Other	32.9	22.5	0.10	20.8	23.5	0.03
APACHE II, mean (SD)[c]	12.1 (3.8)	12.5 (6.2)	0.07	11.0(4.3)	11.0 (4.4)	0.01
Heart rate, mean (SD), beats/min	89.0 (16.8)	102.0 (22.6)	0.65	95.0(18.4)	94.7 (18.5)	0.01
Respiratory rate, mean (SD), breaths/min	30.3 (968.4)[f]	21.9 (6.3)	0.01	23.3 (478.6)[f]	20.6 (5.3)	<0.001
Systolic blood pressure, mean (SD), mm Hg	114.1 (17.1)	118.2 (23.8)	0.20	118.6 (20.1)	118.5 (20.0)	<0.001
Diastolic blood pressure, mean (SD), mm Hg	65.6 (33.9)	68.5 (15.1)	0.11	69.0 (17.5)	68.5 (12.9)	0.02
SOFA score, mean (SD)[d]	6.12 (3.4)	7.07 (3.0)	0.30	6.1 (3.1)	6.0 (2.8)	0.04
Organ dysfunction, %[e]						
Respiration	39.8	78.7	0.86	57.6	60.4	0.03
Coagulation	29.7	27.7	0.05	29.3	26.6	0.03
Hepatic	12.4	22.0	0.26	18.5	18.5	<0.001
Cardiovascular	29.7	27.7	0.05	41.4	41.0	<0.001
Neurologic	22.0	30.8	0.20	26.6	26.5	<0.001
Kidney	28.1	17.9	0.25	13.0	14.5	0.02
Septic shock	19.9	45.6	0.69	29.3	30.8	0.03
Comorbidities, %						
Hypertension	41.7	29.3	0.26	34.9	32.5	0.02
Diabetes	28.9	18.2	0.25	18.9	18.6	<0.001
Coronary artery disease	36.4	7.2	0.76	14.6	12.6	0.02
Stroke	7.6	5.7	0.08	6.3	4.8	0.02
Liver disease	12.5	5.0	0.26	9.6	8.4	0.01
Kidney disease	41.9	2.7	1.07	11.5	8.8	0.03
COPD	6.0	1.5	0.23	3.5	0.9	0.03
Malignant neoplasm	0	1.3	0.16	0	0.5	0.01
Other	0	13.9	0.57	0	1.8	0.02
Admission medications, %						
Glucocorticoids	7.9	13.3	0.18	10.9	10.0	0.01
Anticoagulants	52.7	23.3	0.64	34.1	31.3	0.03

Table 1. *(Continued)*

Variable	Unadjusted			After overlap weighting		
	External control (n = 8,764)	XBJ (n = 911)	ASD	External control (n = 8,764)	XBJ (n = 911)	ASD
Vasopressor	56.5	48.2	0.17	44.9	39.9	0.05
Antimicrobial	88.0	95.3	0.27	91.4	92.7	0.01
Ventilation	92.0	53.0	0.97	73.3	72.7	0.01

Abbreviations: APACHE, Acute physiology and chronic health evaluation; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; SOFA, sequential organ failure assessment; XBJ, Xuebijing injection; ASD, absolute standardized difference. [a] Data for patients included in the propensity-score overlap weighting analysis were multiply imputed. [b] BMI classification: XBJ group were defined according to the Chinese guideline WS/T 428-2013: underweight (<18.5 kg/m²), normal weight (18.5–23.9 kg/m²), overweight (24.0–27.9 kg/m²), and obesity (≥28.0 kg/m²). For the external control group, BMI classification followed the commonly used CDC standards in the United States: underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), and obesity (≥30.0 kg/m²) [c] APACHE II scores range from 0 to 71; 0 indicates the lowest prediction of mortality and 71 indicates the highest. [d] The SOFA score includes sub-scores ranging from 0 to 4 for each of 6 components (respiratory, coagulation, liver, cardiovascular, neurologic, and renal components), with higher scores indicating more severe organ dysfunction. [e] Organ dysfunctions were defined as a SOFA score of 2 or higher for each of 6 components. [f] Certain physiologic variables (e.g., respiratory rate) in the MIMIC-IV cohort displayed extreme values due to data entry or device recording errors, resulting in disproportionately large standard deviations. These values were not excluded a priori; their influence was mitigated by overlap weighting and imputation methods, which are robust to outliers.

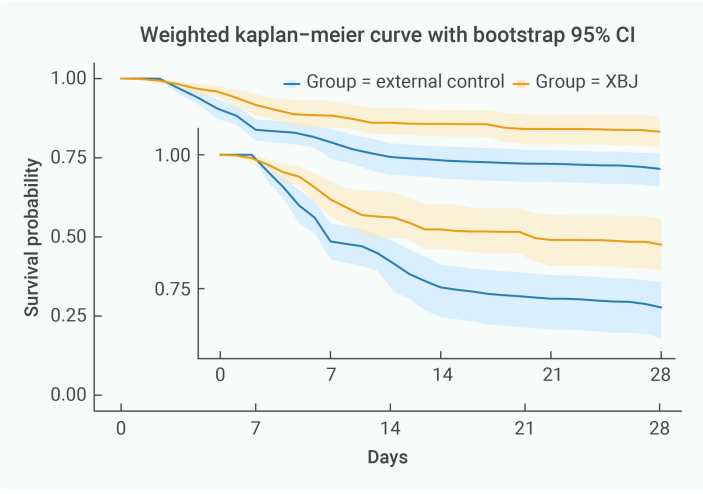


Figure 3. Weighted Kaplan–Meier survival curves with 95% bootstrap confidence intervals, estimated using propensity score overlap weighting.

across both trial and real-world cohorts highlights its potential clinical relevance. The observed efficacy of XBJ may also be biologically plausible. XBJ is a multi-component herbal injection with immunomodulatory, anti-inflammatory, and endothelial-protective properties.[16-18] Unlike previous pharmacologic approaches that targeted single molecular pathways, XBJ's broad-spectrum modulation may better address the complex pathophysiology of sepsis, which involves dysregulated immune responses, coagulopathy, and endothelial injury.[4] This mechanistic profile could explain why XBJ demonstrates benefits in patient populations where prior therapies were ineffective.

Patients in the XBJ group had longer ICU and hospital stays, a finding that requires cautious interpretation. Differences in ICU discharge practices, healthcare resources, and end-of-life decisions between high-income US settings and China could explain these longer stays. For example, cultural norms and clinical policies surrounding critical care may influence the likelihood of withdrawing life-sustaining treatment in non-responders.[19,20] These differences underscore the importance of contextual interpretation when evaluating secondary outcomes across diverse healthcare systems. In addition, the possibility of survivorship bias should be considered. Patients who die early inherently have shorter lengths of stay, whereas patients who survive longer, particularly those recovering from severe shock, are more likely to accumulate additional ICU or hospital days. Importantly, no excess of serious adverse events was observed with XBJ in this study, which argues against delayed recovery or treatment-related harm. Moreover, the safety profile was consistent with findings from two large randomized controlled trials of XBJ, further reassuring its tolerability as a multicomponent herbal formulation. Taken together, the extended stays in the XBJ group are more plausibly explained by improved survival and healthcare practice differences rather than prolonged critical illness, although future studies are warranted to assess more granular recovery and functional outcomes and to further investigate potential treatment effect heterogeneity, including variation by illness severity, intervention timing, or other clinical characteristics.

Cross-population comparisons further support the robustness of our findings. Patients in the XBJ-treated RCT cohort tended to present with greater acute severity, like higher SOFA scores, more frequent respiratory dysfunction, whereas U.S. external controls more often carried chronic comorbidities such as hypertension and coronary artery disease. Despite these differences, the survival benefit remained consistent, suggesting that XBJ's therapeutic effect is not limited to a narrow patient group but may extend across heterogeneous case mixes and healthcare contexts. By applying the EXIT-SEP trial eligibility criteria to a real-world US ICU cohort, this study provides the first patient-level comparative evidence suggesting that XBJ's benefit may extend to Western populations and strengthens the rationale for considering XBJ in future international sepsis guidelines or trial agendas. From a methodological perspective, the use of overlap weighting based on propensity scores, along with consistent findings across alternative adjustment approaches, enhances the robustness of the observed association.[21,22] The application of trial emulation principles prespecified eligibility and exclusion criteria, and multiple imputation for missing data further align with best practices in real-world comparative effectiveness research.[23]

Beyond its clinical benefit, XBJ's low cost (~5 USD per day) makes it a feasible option for routine sepsis care in both high- and low-resource settings. Its affordability could support its adoption in global sepsis management protocols, particularly in resource-limited regions. At the same time, several translational barriers warrant consideration. First, herbal drug standardization is essential to ensure batch-to-batch consistency and regulatory acceptability, particularly under stringent frameworks such as those of the US Food and Drug Administration or the European Medicines Agency. Second, trial preparedness and infrastructure pose challenges, as large-scale randomized trials of traditional Chinese medicines outside China remain scarce and establishing regulatory-grade evidence will require investment in multicenter, internationally coordinated studies. Addressing these challenges will be essential to determine whether XBJ can move from promising evidence to broader regulatory acceptance and clinical adoption.

Table 2. Associations between XBJ use and the death in the crude analysis, multivariable analysis, and propensity-score analyses.

Analysis	Deaths
No. of events/no. of patients at risk (%)	
XBJ group	165/911 (18.11)
Control group	1,358/8,764 (15.49)
Crude analysis, hazard ratio (95% CI)	0.84 (0.71 to 0.99)
Multivariable analysis, hazard ratio (95% CI)[a]	0.52 (0.41 to 0.66)
Propensity-score analyses, hazard ratio (95% CI)	
With overlap weighting[b]	0.48 (0.31 to 0.73)
With inverse probability weighting[c]	0.45 (0.35 to 0.59)
Adjusted for propensity score[d]	0.50 (0.39 to 0.63)
With matching[e]	0.46 (0.32 to 0.67)

[a] Shown is the hazard ratio from the multivariable Cox proportional-hazards model, with adjustment for demographic characteristics, preadmission health status, comorbidities, and medications at admission. The analysis included all 9675 patients. [b] Shown is the primary analysis with hazard ratio from a multivariable Cox proportional hazards model adjusted for the same covariates, with overlap weighting based on the propensity score. The analysis included all patients. [c] Shown is the hazard ratio from the multivariable Cox proportional hazards model, adjusted for the same covariates, using inverse probability weighting based on the propensity score. The analysis included all patients. [d] Shown is the hazard ratio from a multivariable Cox proportional hazards model with the same covariates, additionally adjusted for the propensity score. The analysis included all patients. [e] Shown is the hazard ratio from a multivariable Cox proportional hazards model adjusted for the same covariates, using propensity score matching. The analysis included 1682 patients (841 treated with XBJ and 841 untreated).

Table 3. Secondary outcome.[a]

	External Control (n = 8,764)	XBJ (n = 911)	Difference (95%CI)
Length of stay, mean (SD), d			
In hospital	12.4 (11.4)	16.2 (8.5)	4.0 (2.6 to 5.4)
In ICU	6.7 (6.6)	10.3 (7.3)	3.7 (2.6 to 4.7)

[a] Values are presented as weighted means and standard deviations after adjustment using overlap weighting. Between-group differences were estimated using weighted linear regression models, adjusting for demographic characteristics, preadmission health status, comorbidities, and medications at admission.

This study has several limitations. First, despite rigorous trial emulation and advanced statistical adjustment, residual confounding cannot be entirely excluded because the treatment and control cohorts originated from different healthcare systems with differences in clinical practice patterns, patient genetics, and supportive care. These systemic differences may partly account for outcome variation and should be considered when interpreting the observed survival benefit. An E-value assessment indicated that an unmeasured confounder would need to have a strong association with both treatment assignment and 28-day mortality to explain away the observed association, yet confirmatory evidence from multinational trials remains necessary. Second, XBJ was not available in the MIMIC cohort, limiting our ability to fully replicate the treatment context of the original trial. Third, MIMIC-IV control data reflect clinical practices from 2008 to 2019, which may not fully represent contemporary standards in China or the U.S. Although this temporal gap may affect generalizability, the core elements of sepsis management, early antibiotics, fluid resuscitation, and organ support, have remained relatively stable since the early Surviving Sepsis Campaign guidelines. To further align with the EXIT-SEP protocol, we restricted the cohort to patients who received guideline-recommended therapies within the first 24 hours. The EXIT-SEP enrollment period (2014–2019) overlaps with the later years of MIMIC-IV, which helps mitigate concerns about contemporaneity. Nevertheless, validation in more recent and multinational datasets will be required to confirm generalizability. Fourth, missing data remain an important limitation. Baseline covariates such as BMI had substantial missingness and were addressed using multiple imputation under the assumption of missing at random. For the primary outcome of time to 28-day mortality, patients without a documented death event were assumed to be censored at the time of hospital discharge, without imputation. Both approaches rely on assumptions, specifically missing at random for baseline variables and non-informative censoring for outcomes, and these assumptions may not hold in practice. We did not perform the sensitivity analyses, such as tipping point analysis, to evaluate robustness to violations of these assumptions.[24] Therefore, residual bias due to missing data or censoring cannot be excluded. Fifth, the longer ICU and hospital stays observed in the XBJ group may partly reflect survivorship bias and differences in discharge practices between healthcare systems. We did not conduct formal quantitative analyses to disentangle these factors, and therefore this finding should be interpreted with caution. A further limitation is that all patients in the XBJ trial cohort were of Asian ethnicity, precluding treatment effect analyses stratified by race or ethnicity. Although exploratory summaries of the external control population showed broadly consistent 28-day mortality across racial groups, robust assessment of treatment heterogeneity across diverse populations will require future multinational trials or real-world studies encompassing broader patient diversity.

Despite these limitations, the use of rigorous trial emulation methods and a large, well-characterized ICU dataset enhances the internal validity of our findings, providing a solid foundation for future evaluation of XBJ in non-Chinese populations.

CONCLUSION

This study provides preliminary real-world evidence that XBJ is associated with reduced 28-day mortality among sepsis patients in a non-Chinese ICU population. These findings support the potential generalizability of XBJ's survival benefit beyond the original trial settings and underscore the value of leveraging real-world data with trial emulation principles to evaluate therapies across diverse healthcare systems.

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AUTHOR CONTRIBUTIONS

Study concept and design: Yan Liu, Chi Zhang. Acquisition, analysis, or interpretation of data: Yan Liu, Jing Kang, Chi Zhang, Yixuan Li. Drafting of the manuscript: Yixuan Li, Jing Kang. Critical review of the manuscript for important intellectual content: Songqiao Liu, Haibo Qiu, Chi Zhang. Statistical analysis: Yan Liu, Tianyi Yang. Obtained funding: Chi Zhang, Yan Liu. Study supervision: Chi Zhang, Yan Liu. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

This study was approved by the Ethics Committee of Dongzhimen Hospital, Beijing University of Chinese Medicine (Approval number: 2023DZMEC-294-01). The MIMIC-IV database is publicly available and de-identified, and its use was granted under a data use agreement (Credentialed ID: 59083562). Informed consent was waived due to the retrospective nature of the study and use of anonymized data.

DATA AND CODE AVAILABILITY

No individual, de-identified participant data (including data dictionaries) from this study will be shared. Data are available from the corresponding author upon reasonable request.

SUPPLEMENTAL INFORMATION

It can be found online at https://doi.org/10.59717/j.xinn-med.2025.100164