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# Prognostic Accuracy of Presepsis and Intrasepsis Characteristics for Prediction of Cardiovascular Events After a Sepsis Hospitalization

**Allan J. Walkey, MD, MSc**[1]
**Daniel B. Knox, MD**[2,3]
**Laura C. Myers, MD, MPH**[4,5]
**Khanh K. Thai, MS**[5]
**Jason R. Jacobs, PhD**[2]
**Patricia Kipnis, PhD**[5]
**Manisha Desai, PhD**[6]
**Alan S. Go, MD**[4,5,7–11]
**Yun Lu, MPH**[5]
**Samuel M. Brown, MD**[2,3]
**Adriana Martinez, BA**[5]
**Heather Clancy, MPH**[5]
**Ycar Devis, BS**[1]
**Vincent X. Liu, MD, MS**[4,5]

**OBJECTIVES:** Sepsis survivors face increased risk for cardiovascular complications; however, the contribution of intrasepsis events to cardiovascular risk profiles is unclear.

**SETTING:** Kaiser Permanente Northern California (KPNC) and Intermountain Healthcare (IH) integrated healthcare delivery systems.

**SUBJECTS:** Sepsis survivors (2011–2017 [KPNC] and 2018–2020 [IH]) greater than or equal to 40 years old without prior cardiovascular disease.

**DESIGN:** Data across KPNC and IH were harmonized and grouped into presepsis (demographics, atherosclerotic cardiovascular disease scores, comorbidities) or intrasepsis factors (e.g., laboratory values, vital signs, organ support, infection source) with random split for training/internal validation datasets (75%/25%) within KPNC and IH. Models were bidirectionally, externally validated between healthcare systems.

**INTERVENTIONS:** None.

**MEASUREMENTS AND MAIN RESULTS:** Changes to predictive accuracy (*C*-statistic) of cause-specific proportional hazards models predicting 1-year cardiovascular outcomes (atherosclerotic cardiovascular disease, heart failure, and atrial fibrillation events) were compared between models that did and did not contain intrasepsis factors. Among 39,590 KPNC and 16,388 IH sepsis survivors, 3,503 (8.8%) at Kaiser Permanente (KP) and 600 (3.7%) at IH experienced a cardiovascular event within 1-year after hospital discharge, including 996 (2.5%) at KP and 192 (1.2%) IH with an atherosclerotic event first, 564 (1.4%) at KP and 117 (0.7%) IH with a heart failure event, 2,310 (5.8%) at KP and 371 (2.3%) with an atrial fibrillation event. Death within 1 year after sepsis occurred for 7,948 (20%) KP and 2,085 (12.7%) IH patients. Combined models with presepsis and intrasepsis factors had better discrimination for cardiovascular events (KPNC *C*-statistic 0.783 [95% CI, 0.766–0.799]; IH 0.763 [0.726–0.801]) as compared with presepsis cardiovascular risk alone (KPNC: 0.666 [0.648–0.683], IH 0.660 [0.619–0.702]) during internal validation. External validation of models across healthcare systems showed similar performance (KPNC model within IH data *C*-statistic: 0.734 [0.725–0.744]; IH model within KPNC data: 0.787 [0.768–0.805]).

**CONCLUSIONS:** Across two large healthcare systems, intrasepsis factors improved postsepsis cardiovascular risk prediction as compared with presepsis cardiovascular risk profiles. Further exploration of sepsis factors that contribute to postsepsis cardiovascular events is warranted for improved mechanistic and predictive models.

**KEY WORDS:** bioinformatics; cardiovascular events; missing data; sepsis

Sepsis is defined by the presence of life-threatening organ dysfunction caused by a dysregulated host response to infection (1). Sepsis is the most common and costly illness leading to hospitalization in the United States, resulting in more than 1 million hospitalizations in the United States annually



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(2–5). The combination of increasing sepsis incidence with improved short-term sepsis survival (4, 5) has produced a marked increase in sepsis survivors who often experience new impairments in function, cognition, and health status (6–8).

Sepsis is increasingly recognized as a risk factor for new cardiovascular events, with approximately one-third of sepsis survivors hospitalized for cardiovascular complications in the year following sepsis (9–11). Animal models show that sepsis can rapidly result in atherosclerosis (12), myocardial fibrosis (13, 14), and heart failure (13), similar to long-term exposure to traditional cardiovascular risk factors, but through additional mechanisms of acute inflammation-accelerated atheroma formation, direct infectious myocardial injury, and cardiac fibrosis. Importantly, the relative contributions of presepsis and intrasepsis risk factors that may predispose patients to cardiovascular events following a sepsis hospitalization are unclear.

Identifying the extent to which sepsis characteristics may enhance prediction of subsequent cardiovascular complications above presepsis risk profiles alone is an essential step for evaluating clinical mechanisms of postsepsis cardiovascular complications, developing accurate personalized risk assessments, and testing interventions to reduce cardiovascular complications after sepsis. In this study, we used harmonized electronic health record (EHR) data across two large integrated healthcare systems to evaluate the incremental improvement in cardiovascular risk prediction gained by including intrasepsis factors in addition to presepsis cardiovascular risk assessment among patients hospitalized with sepsis. We hypothesized that intrasepsis variables would add predictive value beyond presepsis factors for postsepsis cardiovascular outcomes.

## METHODS

This study was approved by the Kaiser Permanente Northern California (KPNC, Institutional Review Board [IRB] Number CN-18-3248) and Intermountain Healthcare (IH, IRB Number 1050172) IRBs. A waiver of informed consent was obtained.

### Sepsis Cohort

Using EHR data from two different healthcare delivery systems during two different time spans, we identified adult patients who survived sepsis hospitalization across 21 KPNC (January 1, 2011, and September 30, 2017) and 23 IH hospitals (January 1, 2018, and August 31, 2020). Because the incidence and prevalence of cardiovascular disease increase substantially with age, we limited to patients greater than or equal to 40 years old at time of sepsis, who comprised 96% of adult sepsis survivors. KPNC is a large, integrated healthcare system in Northern California with 230,000 inpatient admissions and 1.4 million emergency visits yearly; IH primarily serves Utah, southern Idaho, and Nevada, with 141,000 inpatient admissions and 512,000 emergency visits annually. In the KPNC cohort, we included patients who had continuous membership (< 30-d gap in membership) the year before and year following sepsis; patients who died during the year following sepsis hospitalization were not excluded. IH is an open health insurance network and therefore did not limit inclusion based on health insurance membership, which may be more subject to loss to follow-up.

We defined sepsis using the Sepsis-3 international consensus definitions, which establishes "suspected infection" based on a timed dyad of antibiotic and culture criteria (with cultures evaluated within 24 hr after first antibiotics or antibiotics started within 72 hr of initial cultures), with sepsis onset at time of first antibiotics or culture (1). Using this definition, we identified patients with Sequential Organ Failure Assessment (SOFA) score (15) of greater than or equal to 2 (or change in baseline ≥ 2) and who had suspected infection within 72 hours of admission. We excluded patients with a prior history of atherosclerotic cardiovascular disease (ASCVD), heart failure or atrial fibrillation within 5 years prior to the sepsis hospitalization as defined in **Table E1** (http://links.lww.com/CCX/A965), and those with length of stay greater than 14 days because they had entered the chronic critical illness phase based on previous research and might have different risk of postdischarge cardiovascular outcomes (16). Patients with multiple sepsis hospitalizations during the study period only had their first hospitalization included.

### Cardiovascular Conditions

All study variable definitions were harmonized across KPNC and IH cohorts. We defined three cardiovascular conditions occurring in the 5 years preceding and 1 year after sepsis using *International Classification of Diseases*, 9th and 10th Edition diagnostic codes based on prior validated conditions: ASCVD, heart failure, and atrial fibrillation

(Table E1, http://links.lww.com/CCX/A965) (17, 18). Patients met criteria for an ASCVD event in the 1 year after sepsis discharge if they had a primary hospital discharge diagnosis of acute myocardial infarction or stroke, primary hospital charge or emergency department diagnosis of peripheral artery disease or a procedure code for a peripheral arterial revascularization procedure or a procedure code for a coronary artery bypass surgery or percutaneous coronary intervention. Patients met criteria for a heart failure event if they had a primary hospital discharge diagnosis of heart failure or primary inpatient diagnosis of heart failure on billing claims. Patients met criteria for atrial fibrillation if they had a primary hospital discharge or emergency department diagnosis of atrial fibrillation or two outpatient diagnoses of atrial fibrillation. All cardiovascular outcomes were measured from clinical encounters occurring after the index sepsis hospitalization. For patients with multiple events, the first was used in all models.

## Predictor Variables

We grouped potential predictors of postsepsis ASCVD, heart failure, and atrial fibrillation outcomes into two categories: 1) presepsis and 2) intrasepsis factors, based on their timing relative to sepsis hospitalization. All models were adjusted for age, race/ethnicity, and sex. **Table E2** (http://links.lww.com/CCX/A965) depicts the types of variables in the models and timing of identification relative to the sepsis hospitalization. We identified presepsis factors as the ASCVD predicted risk estimator calculated based on age, sex, race, smoking status, presence of diabetes, total cholesterol, high density lipoprotein, systolic blood pressure and treatment of hypertension (19), as well as body mass index, Charlson comorbidity score diagnosis groups, smoking history, use of antiplatelet, anticoagulant and statin medications, and chronic kidney disease markers within the prior 5 years up to 1 week prior to sepsis hospitalization. Where multiple values were available, we used the value closest temporally prior to the sepsis hospitalization.

Intrasepsis factors included measures of sepsis-related events during hospitalization including: acute severity of illness based on Laboratory Acute Physiology Score, Version 2 (20) at admission and maximum SOFA score during the hospitalization, most extreme inpatient laboratory values, infection type and site based on Healthcare Cost and Utilization Project Clinical Classification Software (21), receipt of intensive care or life-sustaining therapies, uses of antiplatelet, anticoagulant, corticosteroid, statin medications fluid administration, cardiac ejection fraction, and the proportion of nursing rhythm documentation indicating atrial fibrillation in cardiac rhythm flowsheets (22).

## Missing Variable Imputation

We used imputation to address the missingness across different types of variables (**Table E3**, http://links.lww.com/CCX/A965). Binary variables, like diagnoses, had missing values imputed to zero, indicating patients did not receive these diagnoses. For continuous variables, we compared the final model results of using a simple clinical imputation strategy to impute missing values to the median value of the normal range versus using multiple imputation with chained equations (23, 24). The clinical imputation to normal range strategy was chosen for final analyses because of similar performance to the multiple imputation approach within our data, with simpler harmonization across datasets and greater ease of adoption in practice.

## Statistical Analysis

We used cause-specific Cox proportional hazards models that accounted for death as a competing event and modeled the rate of cardiovascular events in subjects who have not yet experienced either a prior cardiovascular event or death (25). Models were built to evaluate the additional predictive ability of intrasepsis variables for cardiovascular events by first evaluating presepsis variables only, then intrasepsis variables only, and finally, both presepsis and intrasepsis variables. Within each healthcare system, we developed models in a 75% random training dataset, then applied coefficients in a 25% internal test set to internally validate models. We report model performance on the internal test set within each healthcare system for predicting outcomes within 52 weeks after discharge. We compared the performance of models including presepsis only, intrasepsis only, or combined presepsis and intrasepsis variables for predicting cardiovascular events 1 year following sepsis hospitalization for the KPNC and IH cohorts separately. As the primary outcome measure, we compared discrimination (*C*-statistics) across presepsis versus combined presepsis and intrasepsis factor models using Wald statistics based on SEs obtained with an estimate of the influence function (26).

In order to explore the potential for developing a more robust risk prediction in future models using variables available in the EHR, we evaluated predictive performance of the training set model coefficients from KPNC dataset within IH test dataset, and vice versa, as well as model calibration curves. All data analyses were performed in parallel with IH and Kaiser Permanente (KP) cohorts using SAS Version 9.4 (Cary, NC) or in R Version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) (2019).

## RESULTS

Of total hospitalizations (1,062,973 at KP; 308,795 at IH) during the study period, we identified (39,590 at KP; 16,388 at IH) patients whose first sepsis hospitalization met study inclusion criteria (**Fig. 1**). Selected presepsis and intrasepsis characteristics are shown in **Table 1** (full list of characteristics shown in Table E3, http://links.lww.com/CCX/A965; missing data information in **Table E4**, http://links.lww.com/CCX/A965). The median age of the cohort was 70 years (interquartile range [IQR], 60–81 yr) at KP and 66 years (56–76 yr) at IH. The cohort was diverse in terms of sex and race with median ASCVD risk of 11% at KP and 7.5% at IH and a median Charlson comorbidity score of 2 (1–5) at KP and 0 (0–2) at IH. The most common source of sepsis was urinary tract infection (31% at KP and 20% at IH). The median SOFA score at time of sepsis onset was 3 (2–4) at KP and 4 (3–5) at IH.

Among the sepsis survivor cohort, 3,503 (8.8%) at KP and 600 (3.7%) at IH experienced a cardiovascular event within 1-year after hospital discharge, including 996 (2.5%) at KP and 192 (1.2%) IH with an ASCVD event first, 564 (1.4%) at KP and 117 (0.7%) IH with a heart failure event first, and 2,310 (5.8%) at KP and 371 (2.3%) IH with an atrial fibrillation event. Overall, 7,948 (20%) at KP and 2,085 (12.7%) IH patients died within 1 year after sepsis.

Results of the test set models within KPNC and IH are shown in **Table 2**. In all models adjusted for age, race and sex, intrasepsis factors alone had either similar or higher *C*-statistics compared with presepsis factors alone for prediction of postsepsis cardiovascular events. For prediction of cardiovascular events in KPNC data, the *C*-statistic of the combined presepsis and intrasepsis factor test model (0.783 [95% CI, 0.766–0.799]) was larger than the model including only presepsis factors

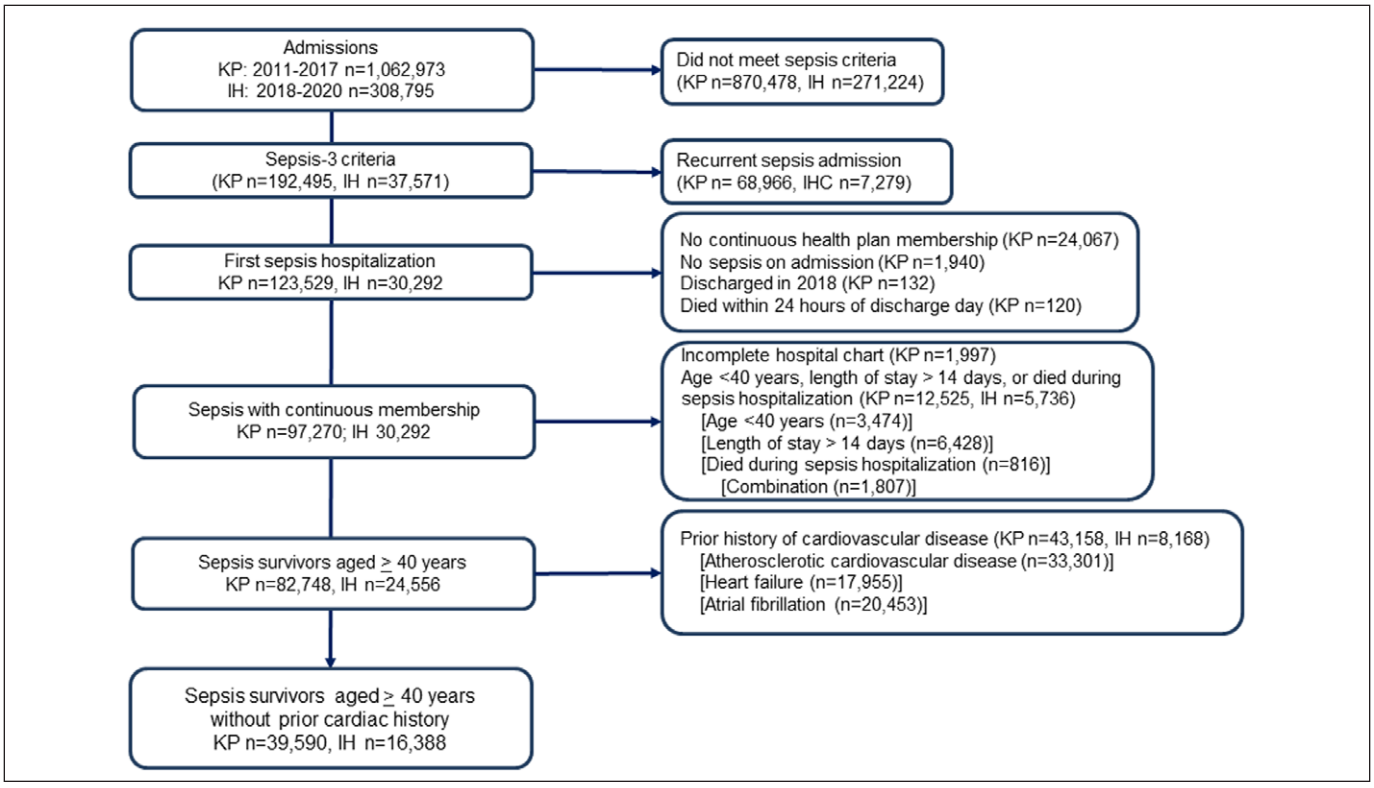


**Figure 1.** Cohort assembly of adults without preexisting cardiovascular disease who survived sepsis hospitalization—Kaiser Permanente (KP) Northern California Intermountain Healthcare (IH). IHC = Intermountain Healthcare.

## TABLE 1.
## Selected Characteristics of Patients Hospitalized With Sepsis Within Kaiser Permanente Northern California and Intermountain Healthcare Systems[a]

| Patient Characteristics | Kaiser Permanente, *n* = 39,590 | Intermountain, *n* = 16,388 |
|---|---|---|
| Demographic variables | | |
| Age at admission | 70.0 (60.0–81.0) | 66.0 (56.0–76.0) |
| Male sex | 18,276 (46.2) | 7,894 (48.2) |
| Race/ethnicity | | |
| Asian/Pacific Islander | 5,301 (13.4) | 200 (1.2) |
| Black | 3,368 (8.5) | 133 (0.8) |
| Hispanic | 5,590 (14.1) | 1,417 (8.6) |
| Native American/Alaska Native | 396 (1.0) | 167 (1.0) |
| White | 24,817 (62.7) | 13,835 (84.4) |
| Other | 118 (0.3) | 636 (3.9) |
| Selected presepsis variables | | |
| Body mass index | 26.91 (23.02–31.97) | 28.3 (24.1–33.6) |
| American College of Cardiology/American Heart Association/ Atherosclerotic Cardiovascular Disease risk[b] | 0.111 (0.031–0.256) | 0.075 (0.026–0.188) |
| Left ventricular ejection fraction, % | 60.0 (60.0–60.0) | 64 (60–68) |
| Charlson comorbidity score | 2 (1–5) | 0 (0–2) |
| Medications | | |
| Antiplatelet therapy (other than aspirin) | 448 (1.1) | 500 (3.1) |
| Aspirin | 685 (1.7) | 477 (2.9) |
| Antihypertensive therapy | 25,897 (65.4) | 2,367 (14.4) |
| Statin therapy | 14,808 (37.4) | 1,345 (8.2) |
| Selected intrasepsis variables | | |
| Treated in ICU | 10,192 (25.7) | 5,461 (33.3) |
| Length of hospital stay, d | 4.0 (2.8–6.0) | 3.4 (2.2–5.2) |
| Cardiac flow sheet with atrial fibrillation | 3,129 (8.1) | 1,100 (6.7) |
| Received hemodialysis while inpatient | 474 (1.2) | 266 (1.6) |
| Total net fluid balance (mL) | 1,480 (–780 to 4,047) | 1,985 (–252 to 4,289) |
| Invasive mechanical ventilation | 2,670 (6.7) | 1,053 (6.4) |
| Noninvasive ventilation | 3,093 (7.8) | 2,480 (15.1) |
| Blood product | 5,785 (14.6) | 1,237 (7.5) |
| Highest Laboratory Acute Physiology Score, Version 2[c] | 89 (63–116) | 103 (83–126) |
| Sequential Organ Failure Assessment score | 3 (2–4) | 4 (3–5) |
| Lowest oxygen saturation (%) | 92 (88–94) | 90 (87,92) |
| Inpatient medications | | |
| Vasopressor | 3,188 (8.1) | 1,538 (9.4) |
| Anticoagulant | 3,480 (8.8) | 2,550 (15.6) |
| Antiplatelet/aspirin | 9,848 (24.9) | 3,127 (19.1) |
| Corticosteroid | 7,905 (20.0) | 5,181 (31.6) |
| Statin | 13,120 (33.1) | 4,220 (25.8) |

[a]The full list of measured variables can be found in Table E3 (http://links.lww.com/CCX/A965).

[b]The American Heart Association/American College of Cardiology pooled Atherosclerotic Cardiovascular Disease risk calculator contains measures of age, sex, race, diabetes, smoking status, total and high-density lipoprotein cholesterol, systolic blood pressure, and treatment for hypertension to estimate 10-yr risk.

[c]The Laboratory-based Acute Physiology Score, version 2 is assigned based on a patient's worst vital signs, pulse oximetry, neurologic status, and 16 laboratory test results in the 72 hr preceding hospitalization.

Median (interquartile range) is reported for continuous variables. Number (percent) is reported for binary/categorical variables. All reported variables are preimputation.

## TABLE 2.

**Cardiovascular Risk Prediction Model Performance for Presepsis, Intrasepsis, and Combined Presepsis and Intrasepsis Patient Characteristics in Test Datasets at Intermountain Healthcare and Kaiser Permanente Northern California Healthcare Systems**

| | | *C*-Statistic (95% CI) | | | |
|---|---|---|---|---|---|
| | | Internal Validation | | External Validation | |
| Outcome | Covariates | IH-Derived Model and IH Test Data | KP-Derived Model and KP Test Data | IH-Derived Model and KP Test Data | KP-Derived Model and IH Test Data |
| Combined cardiovascular events | Presepsis | 0.660 (0.619–0.702) | 0.666 (0.648–0.683) | 0.615 (0.606–0.624) | 0.644 (0.624–0.665) |
| | Intrasepsis | 0.762 (0.724–0.799) | 0.773 (0.756–0.791) | 0.750 (0.740–0.759) | 0.782 (0.764–0.801) |
| | Combined | 0.763 (0.726–0.801) | 0.783 (0.766–0.799) | 0.734 (0.725–0.744) | 0.787 (0.768–0.805) |
| Atherosclerotic cardiovascular disease | Presepsis | 0.627 (0.557–0.698) | 0.672 (0.638–0.705) | 0.598 (0.582–0.615) | 0.648 (0.612–0.684) |
| | Intrasepsis | 0.652 (0.581–0.724) | 0.656 (0.619–0.693) | 0.626 (0.608–0.644) | 0.640 (0.599–0.682) |
| | Combined | 0.661 (0.593–0.730) | 0.691 (0.657–0.726) | 0.618 (0.600–0.636) | 0.653 (0.614–0.692) |
| Heart failure | Presepsis | 0.662 (0.555–0.769) | 0.724 (0.685–0.764) | 0.554 (0.528–0.579) | 0.640 (0.589–0.691) |
| | Intrasepsis | 0.749 (0.663–0.835) | 0.778 (0.743–0.813) | 0.667 (0.644–0.689) | 0.779 (0.733–0.825) |
| | Combined | 0.694 (0.590–0.800) | 0.792 (0.759–0.826) | 0.623 (0.599–0.647) | 0.789 (0.746–0.832) |
| Atrial fibrillation | Presepsis | 0.655 (0.607–0.702) | 0.676 (0.655–0.697) | 0.627 (0.616–0.638) | 0.645 (0.620–0.670) |
| | Intrasepsis | 0.800 (0.754–0.847) | 0.824 (0.805–0.843) | 0.810 (0.800–0.820) | 0.830 (0.808–0.852) |
| | Combined | 0.787 (0.739–0.835) | 0.824 (0.805–0.843) | 0.784 (0.774–0.795) | 0.829 (0.807–0.851) |

IH = Intermountain Healthcare, KP = Kaiser Permanente.

Model performance characteristics within each healthcare system are listed from the test set models using beta estimates from a 75% training set in a 25% random test set sample.

External validated models were performed using model estimates from each healthcare systems training set with test datasets from the other healthcare system.

(0.666 [95% CI, 0.648–0.683]; $p < 0.001$). Similarly, for prediction of postsepsis heart failure events (combined model *C*-statistic 0.792 [95% CI, 0.759–0.826] versus presepsis only 0.724 [95% CI, 0.685–0.764]) and atrial fibrillation (combined model 0.824 [95% CI, 0.805–0.843] vs presepsis only 0.676 [95% CI, 0.655–0.697]), the models with combined presepsis and intrasepsis factors had better discrimination than the models including presepsis factors ($p < 0.001$). However, intrasepsis factors added little to postsepsis ASCVD prediction (combined model 0.691 [95% CI, 0.657–0.726] vs presepsis 0.672 [95% CI, 0.638–0.705]; $p = 0.138$). Results were similar for IH, with improvement in all model *C*-statistics with addition of intrasepsis factors except postsepsis ASCVD risk prediction. Presepsis, intrasepsis, and combined presepsis and intrasepsis models showed similar—generally poor—calibration between observed and predicted event rates (**eFigs. 1*a***, **2*a***, **3**, and **4**, http://links.lww.com/CCX/A965) within the data (eFigs. 1*b* and 2*b*, http://links.lww.com/CCX/A965).

Models from IH and KPNC maintained discrimination performance when externally validated on data from the other healthcare system (Table 2). For example, for combined cardiovascular events the KPNC presepsis model showed similar performance on IH data (*C*-statistic 0.644 [95% CI, 0.624–0.665]) and similar improvement with combined presepsis and intrasepsis factors (*C*-statistic 0.787 [95% CI, 0.768–0.805]; $p < 0.001$ compared with presepsis). Effect estimates for variables included in both models evaluating combined postsepsis cardiovascular event risk are shown in **Table E5** (http://links.lww.com/CCX/A965).

## DISCUSSION

We explored the value of adding sepsis-associated characteristics to presepsis cardiovascular risk profiles for the prediction of postsepsis cardiovascular complications across two healthcare systems. Intrasepsis factors generally showed similar or greater discrimination

as compared with presepsis cardiovascular risk profiles for ASCVD, heart failure, and atrial fibrillation events in the year after sepsis hospitalization. The addition of intrasepsis factors to a comprehensive set of presepsis patient characteristics significantly improved postsepsis cardiovascular risk prediction for combined cardiovascular events, including heart failure and atrial fibrillation following sepsis, but not for ASCVD events. Models showed similar performance across two independent healthcare systems, validating the improved risk prediction generated by inclusion of intrasepsis events in postsepsis cardiovascular risk prediction, and supporting the feasibility of developing generalizable postsepsis cardiovascular risk prediction models. In the future, improved risk models could potentially be used as tools to study screening and treatment strategies that would appropriately identify and mitigate cardiovascular complications after sepsis.

Although prior research has identified sepsis as a potential cardiovascular risk factor (9, 12, 27, 28), few studies have evaluated the incremental value of adding sepsis characteristics as cardiovascular risk predictors. Our findings that intrasepsis factors performed as well as, or better than, presepsis cardiovascular risk predictors and that models combining presepsis and intrasepsis factors substantially improved risk prediction for postsepsis cardiovascular events, raises the possibility that specific characteristics of sepsis may play a role in cardiovascular disease progression. The discrimination of presepsis models for postsepsis cardiovascular events in our models (e.g., validation ASCVD prediction area under the curve [AUC], 0.615–0.644) fell within the range of prior studies of general cardiovascular risk prediction (e.g., pooled ASCVD validation AUCs, 0.556–0.768) (17, 19), suggesting that sepsis did not lower the predictive ability of presepsis factors, but rather, that accounting for sepsis events enhanced 1-year cardiovascular risk prediction. Because our study was designed for risk prediction for sets of patient characteristics occurring in presepsis and intrasepsis timeframes and not causal inference for individual factors, further studies are required to evaluate specific factors associated with postsepsis cardiovascular risk to inform mechanistic hypotheses linking sepsis to long-term cardiovascular risk that may further inform cardioprevention strategies after sepsis.

In our study, model discrimination was highest for the most common postsepsis complication of atrial fibrillation and lower for the less common ASCVD outcomes. Although prior studies demonstrated that elevated troponin during sepsis was a risk factor for postsepsis cardiovascular events when modeled from a causal inference perspective (29), our findings suggest that sepsis-associated clinical measures may not add substantial contributions beyond presepsis risk factors for prediction of postsepsis ASCVD events. Existing research also suggests that atrial fibrillation (30) and heart failure, including septic cardiomyopathy (31), should be formally recognized as organ dysfunction criteria that make up the definition of sepsis itself. However, relatively few studies have evaluated associations between events during sepsis and longer-term cardiovascular complications. Our findings suggest that future, improved prediction models developed to identify high-risk patients who will experience atrial fibrillation or heart failure events after sepsis could be a key step in initiating relevant secondary prevention treatments (e.g., anticoagulation, angiotensin-converting enzyme inhibitors) that may decrease postsepsis cardiovascular sequelae and/or readmission.

Our study has several strengths and limitations. Strengths include using a large, diverse patient cohort across two large healthcare systems with longitudinal follow-up, using a comprehensive array of presepsis and intrasepsis variables, employing robust methods to harmonize data using validated definitions, accounting for missing data, and bidirectional external validation. Limitations include using a high percentage of imputed data for some variables, model calibration that is not currently adequate for clinical use, reliance on administrative codes for diagnosis, the potential for unmeasured variables to alter risk prediction, and potentially different levels of loss to follow-up across the two included healthcare systems that may have resulted in lower cardiovascular event rates in IH that impacted model calibration across health systems. Additionally, we did not compare intrasepsis models to previously validated community atrial fibrillation (32) and heart failure (33) risk prediction models given missing electrocardiogram and fasting glucose data. Analyses were performed only for sepsis present at hospital admission and for patients with lengths of stay less than 14 days; results may not apply to patients with hospital-acquired sepsis or lengths of stay greater than 14 days who may have had cardiovascular events later during a sepsis hospitalization.

In conclusion, across two large healthcare systems, events measured during sepsis hospitalization significantly improved prediction of cardiovascular complications in the year following the hospitalization. Our findings may inform studies to delineate mechanisms of disease and inform development of optimal screening/treatment strategies for postsepsis cardioprotection.

1 *The Pulmonary Center, Department of Medicine, Boston University School of Medicine, Boston, MA.*

2 *Division of Pulmonary and Critical Care Medicine, Intermountain Medical Center, Murray, UT.*

3 *Division of Pulmonary and Critical Care Medicine, University of Utah School of Medicine, Salt Lake City, UT.*

4 *The Permanente Medical Group, Oakland, CA.*

5 *Division of Research, Kaiser Permanente Northern California, Oakland, CA.*

6 *Quantitative Sciences Unit, Stanford University, Palo Alto, CA.*

7 *Department of Health Systems Science, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA.*

8 *Department of Medicine, University of California, San Francisco, San Francisco, CA.*

9 *Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA.*

10 *Department of Medicine, Stanford University School of Medicine, Palo Alto, CA.*

11 *Department of Health Research and Policy, Stanford University School of Medicine, Palo Alto, CA.*

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*Drs. Knox and Liu had full access to data from their respective institutions and takes full responsibility for the accuracy of the analysis. Dr. Walkey conceptualized and designed the study, interpreted results, drafted article, approved final article for submission, and attests to the veracity of the data. Drs. Knox and Myers interpreted the results, finalized the tables/figures, and critically reviewed the article. Dr. Jacobs performed the analysis. Dr. Kipnis designed the statistical analysis and supervised the analysis. Dr. Desai consulted on statistical analysis, interpreted the results, and critically reviewed the article. Dr. Go consulted on the variable input and analysis, interpreted the results, and critically reviewed the article; Ms. Lu performed the analysis; Ms. Martinez prepared the tables and critically reviewed the article; Ms. Clancy prepared the tables and critically reviewed the article; Mr. Devis prepared the figures and critically reviewed the article; Ms. Thai performed the analysis; and Dr. Liu oversaw all parts of the study design, analysis, interpretation, and article preparation.*

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*For information regarding this article, E-mail: allan.walkey@bmc.org*

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