The effect of non-steroidal anti-inflammatory drugs on C-reactive protein levels and mortality in patients with sepsis

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INTRODUCTION

- The role and mechanism of non-steroidal anti-inflammatory drugs (NSAIDs) in sepsis management is unclear. A recent *in vitro* study found that ibuprofen, naproxen, and ketorolac are competitive caspase inhibitors, a promising anti-inflammatory target for septic shock treatment.
- In this study, we characterized the effect of NSAIDs on longitudinal inflammatory responses through C-reactive protein (CRP) levels and on survival in patients with sepsis/septic shock.

METHODS

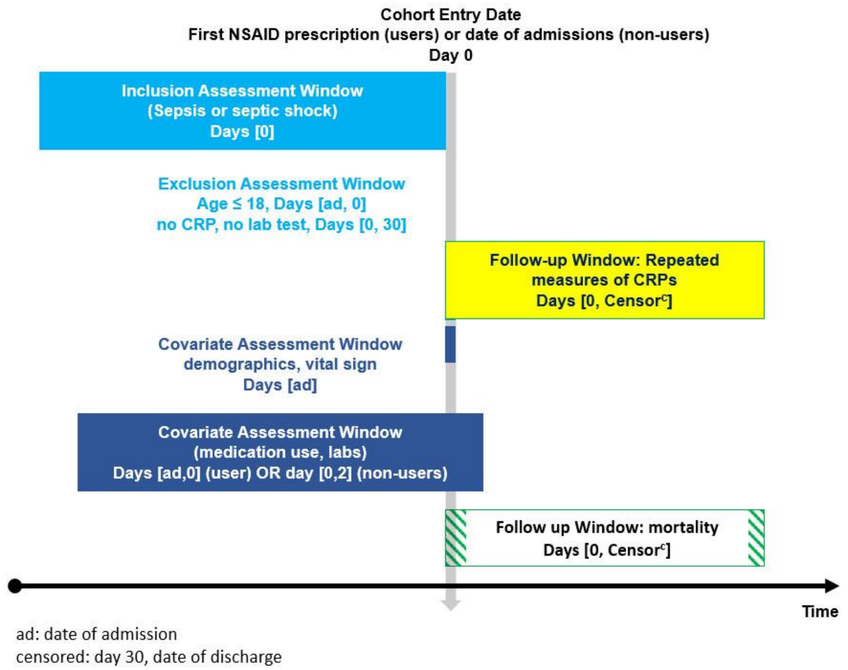

Figure 1. Graphical presentation of study design

Table 1. Components of study design

Components	Description
Data source	Medical Information Mart for Intensive Care-IV (MIMIC-IV) database
Eligibility criteria	*Inclusion*: Aged ≥18, diagnosed with sepsis/septic shock (adapted Angus sepsis definition) admitted to BIDMC 2008-2019. *Exclusion*: no CRP measurement during hospitalization or no other labs
Exposure	Initiation of ibuprofen, naproxen, ketorolac within 10 days after admission
Outcomes	*Longitudinal outcome*: CRP levels (*lab item* code 50889 and 227444) *Survival outcome*: 30-day in-hospital death (all-cause)
Covariates	*Demographics*: age, sex, marital status, ethnicity *Vital signs*: temperature, HR, RR, SpO2, MAP *Labs*: Na, K, HCO_3, Cl, Hb, WBC, PLT, BUN, and SCr *Comorbidities and medication*: CCI, antibiotic, and corticosteroids.
Follow-up	From the index date until death, discharge, or day 30, whichever occurred first
Statistical analysis	Semi-Parametric Joint Modeling of Survival and Longitudinal Data Longitudinal outcome: *linear mixed effects model (LME)* or *non-parametric multiplicative random effects model (NPMRE)*. Survival outcome: Cox proportional hazard model. Data analysis was conducted using SAS 9.4 and R4.2.1

RESULTS

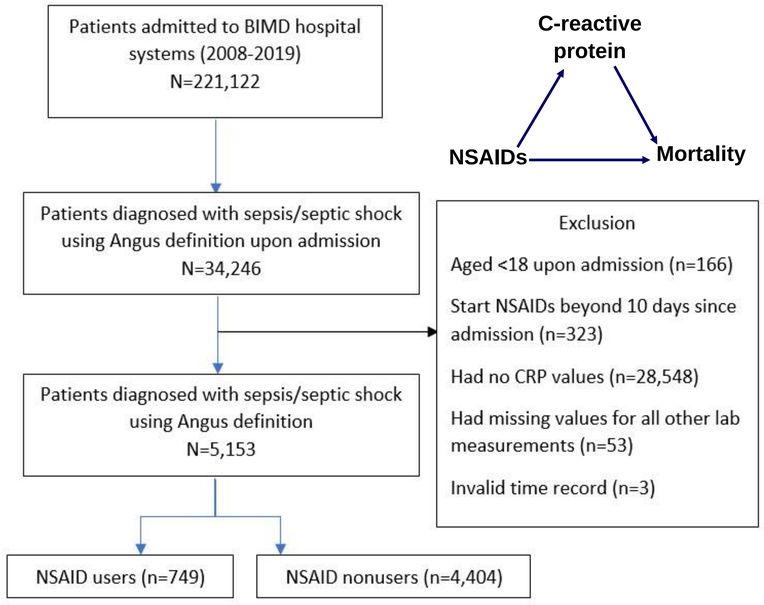

Figure 2. Flowchart of study sample and study conceptualization (top right)

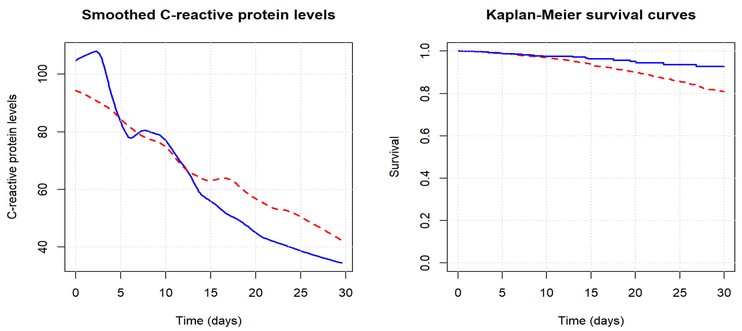

Figure 3. Smoothed mean CRP levels (left) and Kaplan Meier survival curves (right) for patients with sepsis for NSAID users (blue) and nonusers (red).

- In the joint model of LME model, NSAID use was associated with decreased CRP levels overtime ($\beta_{time*NSAIDs}$= -0.92, p=0.04) but not associated with mortality (HR=0.87, 95% CI=0.55-1.39). Increased CRP level was associated with higher mortality (HR=1.005, 95% CI=1.002-1.007).
- The joint model of NPMRE model showed consistent findings: $\beta_{time*NSAIDs\ B\text{-}spline\ 3}$= -0.73, p=0.002; $\beta_{time*NSAIDs\ B\text{-}spline\ 4}$= -0.80, p=0.003. HR_{NSAIDs}=0.89 (95% CI=0.56-1.42), HR_{CRP} = 1.19 (95% CI = 1.03-1.38).
- The joint model of NPMREM showed a better fit to the data visualization and had smaller AIC

Table 2. Characteristics of study sample

	NSAID users (n=799)	NSAID nonusers (n=4404)	p-value
Age	54.51 (17.81)	65.64 (15.43)	<.0001
Female, n (%)	366 (48.87)	1986 (45.10)	0.0555
White, n (%)	496 (66.22)	2977 (67.60)	0.1123
Married, n (%)	271 (36.18)	1840 (41.78)	<.0001
Insurance, n (%) • Medicaid • Medicare • Others	 101 (13.48) 239 (31.91) 409 (54.61)	 306 (6.95) 2170 (49.27) 1928 (43.78)	<.0001
Temperature	36.6 (3.82)	36.54 (3.41)	0.6753
HR	87.35 (17.12)	84.97 (17.28)	0.0005
RR,	18.34 (4.25)	18.40 (3.81)	0.6849
SpO_2	97.65 (2.22)	97.56 (2.69)	0.3130
MAP	88.85 (2.53)	88.18 (1.76)	0.8315
Corticosteroid, n (%)	56 (7.48)	219 (4.97)	0.0048
Antibiotic, n (%)	518 (69.16)	3531 (80.18)	<.0001
CCI	3.87 (2.75)	6.18 (2.94)	<.0001
Na	137.6 (4.43)	137.4 (5.22)	0.1889
K	4.10 (0.57)	4.23 (0.74)	<.0001
Cl	101.7 (5.38)	101.3 (6.19)	0.0836
HCO_3	25.00 (3.76)	23.58 (4.54)	<.0001
Hb	10.18 (1.98)	10.30 (2.09)	0.1597
WBC	10.93 (0.31)	10.93 (0.13)	0.4889
PLT	258.3 (141.8)	236.7 (133.2)	0.0001
BUN	30.65 (23.89)	17.61 (13.24)	<.0001
SCr	1.02 (1.07)	1.81 (1.99)	<.0001

CONCLUSION

- NSAIDs may not have a direct effect on survival but have an indirect effect on survival via reducing CRP levels in patients with sepsis.
- Potential limitations: missing data imputation, unmeasured confounding (SOFA score, ECOG score), confounding by indication.
- Causal interpretation should be cautioned and required further analysis using marginal structural model with inverse probability weighting or g-formula for active control group.

REFERENCES

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