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Association of septic shock definitions and standardized mortality ratio in a contemporary cohort of critically ill patients

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ABSTRACT

Purpose: The newly proposed septic shock definition has provoked a substantial controversy in the emergency and critical care communities. We aim to compare new (SEPSIS-III) versus old (SEPSIS-II) definitions for septic shock in a contemporary cohort of critically ill patients.

Material and methods: Retrospective cohort of consecutive patients, age ≥ 18 years admitted to intensive care units at the Mayo Clinic between January 2009 and October 2015. We compared patients who met old, new, both, or neither definition of sepsis shock. SMR were calculated using APACHE IV predicted mortality.

Results: The initial cohort consisted of 16,720 patients who had suspicion of infection, 7463 required vasopressor support. The median (IQR) age was 65(54–75) years and 4167(55.8%) were male. Compared to patients with old definition, the patients with new definition had higher APACHE III score (median IQR); (73 (57–92) vs. 70 (56–89), $p < .01$); SOFA score; (6 (4–10) vs. 6 (4–9), $p < .01$), were older (70 (59–79) vs. 64 (54–74) years, $p = .03$). They also had higher hospital mortality, N (%) 71, (19.7%) vs. 40 (12.6%), $p < .01$) and a higher SMR (0.66 vs. 0.45, $p < .01$).

Conclusions: Compared to SEPSIS-II, SEPSIS-III definition of septic shock identifies patients further along disease trajectory with higher likelihood of poor outcome.

1. Introduction

The February 232,016 release of the new SEPSIS-III consensus definitions of sepsis and septic shock [1] has provoked significant interest in critical care community. While generally viewed as an enhancement, the new definitions have been received skeptically in several quarters [2]. The American College of Emergency Physicians declined to endorse the current definitions, and both the American College of Chest Physicians [2] and the Latin American Sepsis Institute [3] have released statements opposing the re-definition.

The older definition relied on the concept of "Systemic Inflammatory Response Syndrome," (SIRS) a sensitive but nonspecific set of symptoms associated not only with inflammation, but with critical illness in general. When coupled with a clinical suspicion of infection, this comprised the 1992 consensus definition for sepsis [4]. As pointed out in a recent critical editorial "[the definitions,] though imprecise, provide a useful framework for clinical intervention." Importantly, since the adoption of these definitions, sepsis mortality has decreased [2].

In the SEPSIS-III definition of septic shock, SIRS has been abandoned [5]. In addition to suspicion of infection, qSOFA and the use of vasopressors to maintain mean arterial pressure of at least 65 mmHg after initial fluid resuscitation, the new definition added the requirement for elevated lactate (>2 mmol/L). The new definition is associated with high hospital mortality (40%) [5].

While this work supports the construct for the new septic shock definition, and it has been formally compared to 1992 consensus definition, these recent studies have not taken into account the patients who overlap, meeting both definitions [6,7]. To systematically assess the differences between the new and old definitions for septic shock, we conducted a retrospective cohort study to directly compare clinical

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characteristics and outcomes of critically ill septic shock patients based on these definitions.

2. Materials and methods

2.1. Study design

The retrospective study has been approved by the approved by the Mayo Clinic institutional review board and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All included patients or their legally authorized representative has provided a prior research authorization allowing their already existing medical records to be used for research purposes.

2.2. Study patients

We included all index admissions of consecutive adult patients (age ≥ 18 years) to adult critical care settings (medical intensive care unit (ICU), coronary care unit, thoracic/vascular ICU, mixed medical/surgical ICU, cardio-surgical ICU and the neuro-critical care ICU) at Mayo Clinic Hospital in Rochester, Minnesota between January 1, 2009 and October 31, 2015 (at the time of new sepsis definitions announcement our dataset was completed till this date). We excluded patients who underwent elective surgeries prior to ICU admissions, as well as patients admitted to the pediatric and neonatal ICUs. We focused on patients requiring ICU admission thus only septic shock patients were included in the cohort.

2.3. Definitions

We defined suspected infection based on the combination of antibiotics (parenteral and/or oral) and body fluid cultures. The combination of cultures and antimicrobials had to occur within a predefined window depending on if cultures or antibiotics were initiated first. If antibiotics were administered first, culturing had to occur in the next 24 h for inclusion. If cultures were obtained first, antibiotic initiation in the next 72 h qualified [8]. We defined septic shock as patients with suspected infection, meeting 2 SIRS criteria and having persistent hypotension (mean arterial pressure < 65 mmHg) requiring the use of vasopressors and having a serum lactate level of >2 mmol/L despite adequate volume resuscitation [1]. We defined SIRS, severe sepsis and septic shock as sepsis guidelines, 2001 [9] and SEPSIS-III per the new consensus statement.

2.4. Data collection

We identified patients who were admitted to the ICU through a validated prospective electronic medical records database (EMR) that retrieves variables for all the ICU patients in near real-time known as the "ICU Data Mart". We collected demographics including the age, gender, ICU admission/discharge times, vital signs including (Respiratory rate, heart rate, temperature and blood pressure), use of invasive/non-invasive ventilation, APACHE III and SOFA scores and ICU/hospital mortality using the ICU Data Mart. The steps of the development of the database, date security and validation of the demographics have been previously reported [10].

We collected data on lab values including serum lactate, antibiotics and blood culture prior to ICU admission and do not intubate/do not resuscitate (DNI/DNR) status at admission using the United Data Platform (UDP), the clinical data repository for Mayo Clinic [11]. The UDP is an exhaustive clinical data warehouse that stores patient demographics, diagnoses, and hospital, laboratory, flow sheets, clinical, and pathological data gathered from various clinical and hospital source systems within the institution. Advanced Cohort Explorer (ACE) was used to access the data contained within the UDP. ACE is an interface for UDP which can look for patient information including their demographics, flow sheets, laboratory data, clinical notes etc. The data in ACE is obtained from multiple clinical and hospital source systems within Mayo Clinic, Rochester and is supported by Mayo Clinic Information technology (IT) department. Regular user auditing, purpose/protocol checks are done to maintain the patient data security and confidentiality and ACE also compliant to the HIPAA, State law and Mayo Clinic policy to the retrieval of all patient data [12]. We manually reviewed a random sample of 200 patients for quality assurance, which included review of individual components as well as entire concepts of the Sepsis-III definitions.

2.5. Outcomes

Our primary outcomes were ICU and hospital mortality. Our secondary outcomes consisted of ICU and hospital length of stay.

2.6. Statistical analysis

We expressed data as median (interquartile range) for quantitative variables and as frequency (percentage) for qualitative variables. We analyzed all the patients with new and old septic shock for the primary and secondary outcomes of ICU/hospital mortality and ICU/hospital length of stay. One-way Analysis of Variance (ANOVA) test was used for comparing means of four groups. We assessed group differences for categorical data (sex, DNR/DNI, invasive/non-invasive ventilation, ICU/hospital mortality, discharge to home) using the chi-square test while two sample *t*-test (age) or Kruskal-Wallis test (APACHE III at 24 h, SOFA day-1, ventilation days, ICU/hospital length of stay) to compare continuous variables.

We calculated the Standardized Mortality Ratio (SMR) using previously validated APACHE IV [13] predicted morality for each of the four sepsis definition classes (none, old, new and both). For Primary analysis, the 'both' definition group was separated out to maintain 'old' and 'new' groups mutually exclusive. Specifically, the number of actual hospital deaths was the numerator, and the denominator was the number of expected deaths – based on APACHE prediction of mortality [14]. Univariate comparison of the SMRs, among the 4 definition classes, was carried out using a Poisson regression model with a log link. The observed deaths were the outcome, the expected deaths were an offset term and the four definition classes were represented by an indicator variable. The overall *P* value is based on the likelihood ratio test which was used to determine if the SMRs were similar.

We performed further analyses using the multivariate logistic regression to control for the effect of DNR/DNI status of the patients and APACHE III and SOFA day-1 scores on the hospital mortality for both old and new definitions of septic shock. We adjusted with APACHE III and SOFA day-1 to limit the possibility of any residual confounder and for better prediction of outcome. We summarized associations between outcomes of interest and predictors as odds ratios (OR) and 95% confidence intervals (CI). We considered all tests were two sided and *p*-values of <0.05 statistically significant. We used JMP 13.0.0 (SAS Institute Inc., Cary, NC, U.S.A.) software for all statistical analyses.

3. Results

The cohort started with total 94, 280 adult ICU admissions from January 2009 to October 2015. Following application of our exclusion criteria, a large number of patients were excluded because of no research authorization, multiple admissions, no suspected infection and elective surgeries (Fig. 1), we had 7463 index admissions to ICU with research authorization, suspected infection, and vasopressor requirements. A total of 2690 (36%) patients met criteria for both definitions, 3256 (44%) patients met only the criteria for the old definition, 361 (4.8%) met only the criteria for new definition and 1156 (15%) patient had infection and shock but met neither old nor new criteria (Fig. 1). The patients who met both definitions had higher APACHE and SOFA

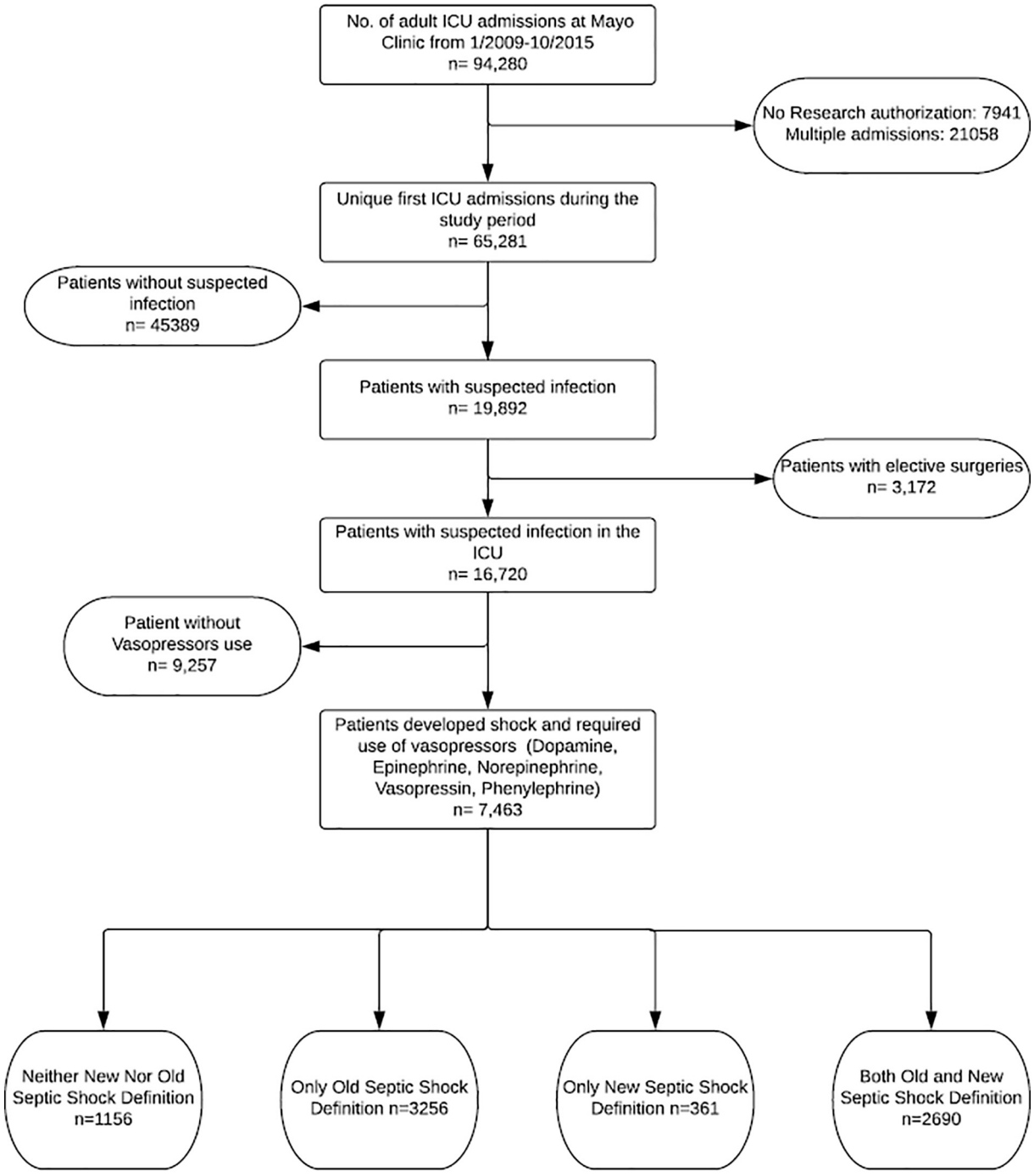

Fig. 1. Flowchart of Included Patients.

scores, and were more likely to have limited resuscitation preferences (DNI/DNR) compared to the other groups (Table 1 and Fig. 2). They also had higher ICU and hospital mortality, and had a higher standardized mortality ratio (Table 1). In a direct comparison of those meeting new (those meeting new only and both) versus only those meeting the old definition (and thus missed by SEPSIS-III), patients were older, more likely to express limited resuscitation preferences, and had a higher APACHE-III and day-1 SOFA scores. They also had worse ICU and hospital mortality, higher standardized mortality ration, and lower number of ICU-free days. (Table A. electronic data supplement). Similar results were observed in various subset analyses, when restricted to only Medical ICU patients (Table B and C. electronic data supplement).

In multivariate logistic regression after adjusting for DNR/DNI status of the patients and APACHE III and SOFA day-1 scores, Sepsis-III definition was associated with higher odds of hospital mortality, OR = 1.69 (95% CI 1.46–1.96).

4. Discussion

In this single center retrospective cohort study, when compared to SEPSIS-II the patients meeting SEPSIS-III septic shock definition had higher severity of illness, were more likely to have limited resuscitation preferences at the time of ICU admission and worse standardized mortality ratio. Notably, sizable number of patients with shock and infection did not meet criteria for either new or old definition.

Table 1
Baseline characteristics and outcomes in cohort of critically ill patients with old vs. new septic shock definitions.

Patient characteristics	Neither new nor old septic shock definition ($N = 1156$)	Only old septic shock definition ($N = 3256$)	Only new septic shock definition ($N = 361$)	Both old and new definition ($N = 2690$)	p-Value[b]
Age in years, median (IQR)	64.9 (56–75)	64.3(53.7–74.7)	69.4(59–79)	64.8 (54–75)	<0.001
Sex, male N (%)	652 (56.4)	1798(55.2)	224(62.04)	1493 (55.5)	0.09
DNR/DNI, N (%)	113 (9.8)	383 (11.8)	66 (18.3)	489 (18.3)	<0.001
APACHE III score, median (IQR)	62 (50–77)	70(56–89)	73(57–92)	85 (68–108)	<0.001
SOFA day-1, median (IQR)	5(2–7)	6(4–9)	6(4–10)	9 (6–12)	<0.001
SIRS, N (%)	0 (0)	3256 (100)	0 (0)	2690 (100)	<0.001
Highest lactate in 24 h, median(IQR)	1.2 (0.8–1.5)	1.3 (1–1.6)	2.8 (2.1–4.4)	3.3. (2.3–5.2)	<0.001
Invasive mechanical ventilation, N (%)	525 (45.4)	1967(60.4)	222(61.5)	1931 (71.8)	<0.001
Total vent days, median (IQR)	1.2 (0.3–4.4)	1.9 (0.5–5.5)	1.7 (0.5–5.1)	2.4 (0.8–6.3)	<0.001
ICU LOS, days median (IQR)	2.1 (1–5.1)	3.07(1.6–6.9)	3.35(1.2–7.1)	3.7 (1.8–7.86)	<0.001
Hospital LOS, days median (IQR)	11.3 (6.9–19.8)	12.3(7.3–21.2)	11.96(6.5–22.2)	11.4 (5.9–21.2)	<0.001
ICU mortality, N (%) median (IQR)	40 (3.5)	239 (7.34)	42 (11.6)	516 (19.2)	<0.001
Hospital mortality, N (%)	93 (8)	409 (12.6)	71 (19.7)	748 (27.8)	<0.001
ICU free days, median (IQR)	6.1 (3.1–12)	6.2 (3–12.3)	5.8 (2.3–14)	4.9 (0.9–11)	<0.001
APACHE IV predicted hospital mortality, Median (IQR)	0.13 (0.06–0.26)	0.22 (0.1–0.4)	0.22 (0.1–0.45)	0.34 (0.17–0.62)	<0.001
Standardized mortality ratio[a]	0.42	0.45	0.66	0.69	<0.001

Data is expressed as median (Interquartile range) or as number (percentage).
[a] Observed divided by expected (APACHE IV predicted) mortality.
[b] OneWay ANOVA test for four groups Comparison.

Although lower than previously reported [8], hospital mortality of patients meeting only new septic shock definition was high (19.7%) and for the group who met both definitions it was even higher (27.8%) and both were higher than in patients meeting only SIRS-based definition (12.6%). Our data confirms the high specificity but poor sensitivity of the new definition of septic shock. The new definition was only able to classify fewer (~48% less) patients with septic shock ($N = 3051$) as compared to older definition ($N = 5946$). A large number of patients didn't meet criteria for the new definition of septic shock as they did not have lactate >2 mmol/L. It is highly plausible to have hypotension with or without meeting the lactic acidosis requirement. For example, a clinician may reasonably determine that a patient with pneumonia, fever, tachycardia and blood pressure of 80/50 has septic shock even if the lactate was 1.6 mmol/L after fluid resuscitation.

A novel finding in our study is that Standardized Mortality Ratio (SMR) [15] is significantly higher in patients diagnosed with new definition. For SMR calculations, severity scores used in the ICU do not include lactate, but serum lactate has shown association with mortality in severe sepsis independent of shock status and organ failure [16]. Serum lactate is a marker of localized tissue hypoxia, not truly a marker of inflammation; and has a direct correlation with increased morbidity and mortality [17]. Prior analyses of the surviving sepsis database have shown a higher mortality in patients with elevated lactate levels, with or without hypotension [18]. Hence, it's not surprising to see that inclusion of lactate in the new definition better correlates with mortality [1]. As part of the goal of the new definition was to identify the patients at highest risk for poor outcome, this classification schema is ultimately reasonable for a research based definition.

In a more clinically oriented sense, SEPSIS-III omits patients with septic shock likely to benefit from early recognition. A clinically oriented definition would identify patients who would be most likely to benefit from early intervention, not just those who are likely to have poor outcomes. Sepsis bundles, using the old definition, have demonstrated success in arresting severity of illness among septic shock patients. As elegantly demonstrated by Miller et al., the adherence to early components of sepsis bundle (i.e. recognition, early antibiotics and fluid) can halt disease progression and eliminate the need for later components of the bundle [19]. Thus, hospitals with early and appropriate management of septic shock patients may not be credited for preventing further progression of disease and worsening organ failure under the new,

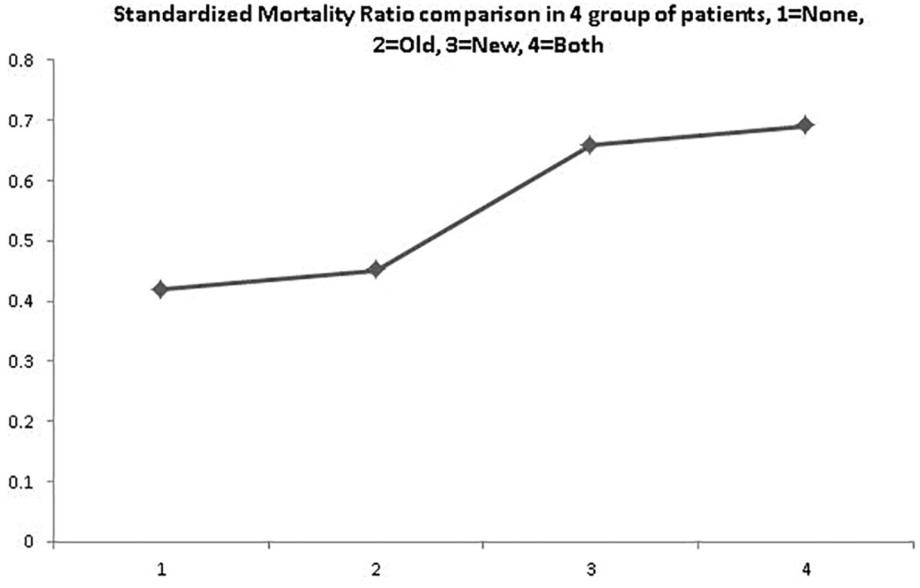

Fig. 2. Standardized Mortality Ratio (SMR) plotted against 4 groups of patients.

research-themed schema. The new definition's impact on SMR will only reflect patients who are already progressing further down the path towards deterioration. This may owe in part to the lactate requirement in the new definition biasing this towards finding late sepsis cases. As the response from the Surviving Sepsis Campaign to Sepsis III [20] and editorial from American College of Chest Physicians (ACCP) journal CHEST have emphasized [3] that early identification and timely aggressive intervention remains paramount. Whether or not redefining sepsis and septic shock will lead to clinical differences and further reduction in mortality remains to be seen.

Of note, both SEPSIS-II and SEPSIS-III definitions leave unaccounted a significant minority of patients with infection and shock meeting neither criteria (Fig. 3).

As previously noted [21], these patients have lower, but still substantial mortality and deserve further evaluation. Sepsis is an evolving definition, and SEPSIS-III may not be the final stage in that evolution. SEPSIS-III highlights the role of infection induced organ dysfunction and identifies a more morbid group of patients by redefining septic shock with a high lactate value. As pointed out in an accompanying editorial in the initial release, the definition of sepsis still relies on a subjective suspicion of infection. The role of novel technologies for rapid microbiological diagnostics such as matrix-associated laser desorption ionization–time of flight or polymerase chain reaction (is not discussed, and this will certainly have to be addressed in future sepsis definitions as technology and our understanding of pathophysiology advances [22]. This is a common deficit between both definitions of sepsis, however, and cannot be used to dismiss the current definition. Of note, Sepsis-III definition has not yet been adopted in our Emergency Department / ICU sepsis protocols.

Our study's main strength is the independent validation of new septic shock definition. Inclusion of patients meeting both old and new definitions as exclusive group makes it unique read. Our patient population is distinct from the populations used in deriving the sepsis III definition, and none of the investigators were involved with either Sepsis II or III definitions or revisions. One another strength is that our study consists of a large cohort, derived from previously validated [23-26] automated near-real time ICU database [10] that prospectively collects pertinent data in critically ill patients. A rigorous manual validation of newer definition is performed among various subgroups of critically ill patients. The high data quality assured the validity of both septic shock definitions.

There are several limitations of our study. Being observational in nature, the data collected were restricted to clinically measured variables and some patients may not have had pertinent measurements (lactate) at all time points, potentially missing elevated values. APACHE methodology recalibration has not been taken in account. Because of our focus on sepsis patients requiring ICU admission, non septic-shock patients are not part of this manuscript. Due to a single center design and predominantly Caucasian population these findings lack generalizability [27]. Finally, despite rigorous validation, electronic medical record data can contain errors that cannot be apparent by retrospective review.

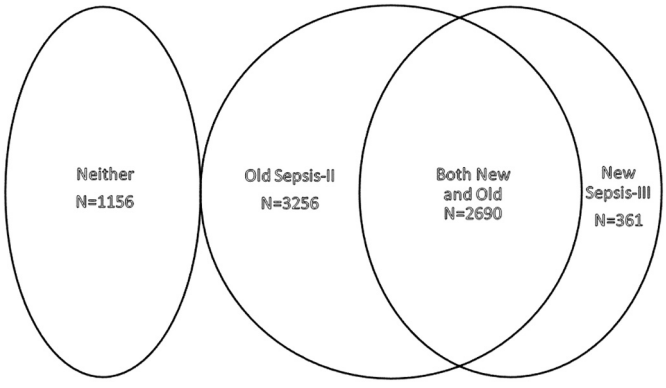

Fig. 3. Venn Diagram of patients meeting no definition, only old definition, only new definition and both old and new definition.

5. Conclusion

In conclusion, in a large contemporary cohort of critically ill patients, those meeting the new septic shock definition had higher severity of illness, higher mortality, and worse standardized mortality ratio, when compared to patients meeting the old definition of septic shock. A significant minority of patients with infection and shock meet neither criterion. The differences in standardized mortality ratios can have implications for quality improvement and performance measures as the new definition identifies patients further along disease trajectory with the missed opportunity for early and adequate treatment.

Author contributions

RK, TDS, JCO, GW, HR and OG had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: RK, TDS, JCO, OG. Acquisition, analysis, or interpretation of data: RK, TDS, JCO, GW, HR, PB, OG. Drafting of the manuscript: RK, TDS, JCO, GW, HR and OG. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: RK, TDS, HR, JCO, PB, OG.

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Conflict of interest

No conflict of interest is reported by any of the co-authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.01.005.

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