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# Mortality Associated with Severe Sepsis Among Age-Similar Women with and without Pregnancy-Associated Hospitalization in Texas: A Population-Based Study

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Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
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Literature Search F  
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**Background:** The reported mortality among women with pregnancy-associated severe sepsis (PASS) has been considerably lower than among severely septic patients in the general population, with the difference being attributed to the younger age and lack of chronic illness among the women with PASS. However, no comparative studies were reported to date between patients with PASS and age-similar women with severe sepsis not associated with pregnancy (NPSS).





**Material/Methods:** We used the Texas Inpatient Public Use Data File to compare the crude and adjusted hospital mortality between women with severe sepsis, aged 20–34 years, with and without pregnancy-associated hospitalizations during 2001–2010, following exclusion of those with reported chronic comorbidities, as well as alcohol and drug abuse.

**Results:** Crude hospital mortality among PASS vs. NPSS hospitalizations was lower for the whole cohort (6.7% vs. 14.1% [ $p < 0.0001$ ]) and those with  $\geq 3$  organ failures (17.6% vs. 33.2% [ $p = 0.0100$ ]). Adjusted PASS mortality (odds ratio [95% CI]) was 0.57 (0.38–0.86) [ $p = 0.0070$ ].

**Conclusions:** Hospital mortality was unexpectedly markedly and consistently lower among women with severe sepsis associated with pregnancy, as compared with contemporaneous, age-similar women with severe sepsis not associated with pregnancy, without reported chronic comorbidities. Further studies are warranted to examine the sources of the observed differences and to corroborate our findings.

**MeSH Keywords:** **Hospital Mortality • Multiple Organ Failure • Pregnancy • Sepsis**

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## Background

Pregnant women have an increased risk of infection related to the physiological and anatomical changes in obstetric patients [1], as well as due to a complexly modulated immune response in pregnant women, with the latter associated with increased susceptibility to and severity of illness from certain pathogens [2]. Pregnancy-associated severe sepsis (PASS) is a rare complication in high-resource countries [3,4]. However, the initial diagnosis of PASS is often challenging [5,6], its clinical course can be rapidly fatal [5], and PASS is presently a major cause of maternal death [6]. Thus, although the majority of pregnant women are healthy, the case fatality rate of PASS at the population level may be expected to exceed that of their non-obstetric, age-similar, healthy, severely septic female counterparts. However, the reported hospital mortality associated with PASS, varying between 1.4% [7] and 12% [4] in population-based studies, is markedly lower than among severely septic patients in the general population [8,9]. Because severe sepsis mainly involves older adults in the general population [8,9], it has been suggested that the lower mortality noted among severely septic obstetric patients is due to confounding factors of younger age, lack of chronic comorbid conditions, and predominance of possibly more readily manageable genital tract infections [1]. However, there have been no reports to date, to the best of our knowledge, comparing the mortality rate among PASS patients to that among age-similar women with severe sepsis not associated with pregnancy (NPSS). Thus, while pregnancy appears to be associated with increased predisposition and possibly adverse response to infection [2], the impact of pregnancy on mortality among severely septic women remains uncertain.

We sought to compare hospital mortality associated with PASS with that among contemporaneous, age-similar women with NPSS, without reported chronic comorbid conditions, using population-level data in Texas, and hypothesizing comparable or higher mortality among the former.

## Material and Methods

### Setting and data sources

The Texas Inpatient Public Use Data File (TIPUDF) was used to perform a retrospective, population-based cohort study of severe sepsis among women in the state during the years 2001–2010. The TIPUDF is an administrative data set maintained by the Texas Department of State Health Services [10]. The use of the data set has been previously described [11]. Briefly, TIPUDF includes detailed de-identified inpatient discharge data on the demographic, clinical, resource utilization, and outcome domains from all state-licensed hospitals, with

the exception of those exempt by state statute from reporting to the Texas Health Care Information Collection. Exempt hospitals include: a) those that do not seek insurance payment or government reimbursement, and b) selected rural providers, based on bed number and local county population [8]. The facilities included in the mandated report to TIPUDF account for 93% to 97% of all hospital discharges in the state. US Census Bureau data [12] were used to derive information on data on the proportion of residents living below the poverty line of the population residing at the zip code of identified hospitalizations. The Institutional Review Board of Texas Tech Health Sciences Center has determined that the present study is exempt from formal review due to use of publicly available, de-identified data.

### Study population

We identified all hospitalizations in the TIPUDF data set among women aged 20–34 years who did and did not have pregnancy-associated hospitalization, and who had reported diagnosis of severe sepsis during the study period. We chose the age group of 20–34 years among pregnancy-associated hospitalizations to minimize confounding, because both older age [13] and teen pregnancy [14,15] have been associated with worse maternal outcomes, including increased mortality. Pregnancy-associated hospitalizations were identified using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes: (see Supplementary Table 1). Hospitalizations with severe sepsis were identified based on the approach described by Lagu et al. [9] and were defined as those with a primary or secondary diagnosis of: 1) specific codes of severe sepsis (995.92) or septic shock (785.52), and/or 2) a combination of an infectious process (see Supplementary Table 2) and 1 or more organ failures (see Supplementary Table 3). Assessments of patients' severity of illness were based on the number of failing organs, as described by Kumar et al. [8]. We used both primary and secondary diagnoses of severe sepsis, because it is often a complication of hospitalization for another primary condition (i.e., severe sepsis complicating delivery).

We excluded women with reported chronic comorbid conditions described under the Deyo modification of the Charlson Comorbidity Index [16], as well as those with reported drug or alcohol abuse. We did not exclude hospitalizations with reported obesity because obesity, which involves more than 1 in 4 obstetric patients [17] and is present in about 1 in 3 women aged 20–39 in the United States [18], is substantially under-reported in administrative data sets of obstetric patients, with [3] and without [19] severe sepsis, and in the general population [20]. Indeed, excluding reported obesity hospitalizations in the present study would be likely to leave most unaccounted for. Thus, the cohort used in the present study, following the aforementioned exclusions of age, chronic comorbidities,

and alcohol and drug abuse, represents all reported statewide hospitalizations with PASS and NPSS.

### Data collection

The collected data domains included women's ages, race/ethnicity, type of health insurance, zip code at area of residence, obesity, sites of infection (see Supplementary Table 4), number and type of organ failures, use of mechanical ventilation and hemodialysis (see Supplementary Table 5), and admission to an ICU (defined as presence of an Intensive Care Unit charge greater than \$0). Although selected microbiology data are included in administrative data sets, they are not reported in the majority of hospitalizations of severely septic patients [21]. In addition, we identified more than 1 site of infection in some hospitalizations in both groups. However, the source of reported microbiological data and use of sterile site sampling cannot be ascertained, as this information is not included in administrative data sets. The aforementioned constraints can lead to skewed information with inappropriate internal and external validity. We thus elected to not report microbiology information in the present cohort.

### Outcomes

Hospital mortality was the primary outcome. Secondary outcomes included the number and type of failing organs.

### Data analysis

Severe sepsis events were described as number of hospitalizations due to use of discharge-level data in TIPUDF, thus not identifying individual patients.

In addition to using the number of organ failures as a surrogate measure to compare disease severity, we further compared the severity of selected individual failing organs between PASS and NPSS hospitalizations, through examination of the rate of use of mechanical ventilation among severe sepsis hospitalizations with respiratory failure, and rate of use of hemodialysis among those with acute renal failure.

The deaths associated with PASS and NPSS were examined as hospital mortality. In order to examine the robustness of observed differences of hospital mortality for the whole cohort, we performed exploratory subgroup analyses comparing mortality between PASS and NPSS hospitalizations among those with  $\geq 3$  organ failures and women with reported infections of the respiratory tract, with no other concomitantly reported site of infection. The subgroups were chosen to assess differences in mortality among patients with a more severe subset of severe sepsis, and among those with an infection site reported to be associated with increased risk of death among severely

septic patients [22], with the latter subgroup also used to compare mortality among women without genital tract infection.

Because a substantial number of severe sepsis hospitalizations had more than 1 reported site of infection and nearly 1 in 2 women with PASS had reported genital tract infection, while the corresponding number among NPSS hospitalizations for the latter was less than 1%, an adequate matched comparison between PASS and NPSS groups could not be performed. Although there have been no reports of age-related rising hospital mortality among young, otherwise healthy women with severe sepsis within the examined age range, we included age in adjustment for covariates between examined PASS and NPSS groups due to imbalance in age subgroup distribution. We used the Mantel-Haenszel test to derive adjusted odds ratios for mortality among PASS vs. NPSS hospitalizations for the whole cohort and the exploratory subgroup analysis of those with reported  $\geq 3$  organ failures. Adjusted mortality rate was not examined for the subgroup with respiratory tract involvement, because the only reported site of infection due to a very low number of deaths among PASS hospitalizations in this subgroup precluded a valid risk-adjusted exam. The derived mortality odds for the whole cohort and those with  $\geq 3$  organ failures were adjusted for age, race/ethnicity, health insurance, level of poverty, obesity, and number of failing organs (the later covariate was not included in analysis of the subgroup with  $\geq 3$  organ failures). The common presence of more than 1 site of infection in both groups precluded use of infection site as a covariate in deriving adjusted mortality odds ratios.

The data were examined for normality of distribution using the Kolmogorov-Smirnov test. Categorical variables were reported as numbers (percentages). Continuous variables were described as mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables, as appropriate. Group comparisons were performed using a 2-sided  $\chi^2$  test for categorical data and a t-test or Mann-Whitney *U* test for continuous covariates, as appropriate. Adjusted odds ratios (aOR) and 95% confidence intervals (95% CI) were calculated.

We used SAS version 9.3 (SAS Institute, Cary, NC, USA) and MedCalc version 15.6 (MedCalc Software, Ostend, Belgium) software for data analyses. A 2-sided *p* value  $< 0.05$  was considered significant.

## Results

There were 449 PASS and 1874 NPSS hospitalizations of women aged 20–34 years during the study period, following exclusion of those with reported chronic comorbidities, and alcohol and drug abuse. The demographic characteristics, health insurance, sites of infection, rates of ICU admission, and the

**Table 1.** Comparative demographic, poverty at zip code of residence, and health insurance features among severely septic women with and without pregnancy-associated hospitalizations.

Variable	PASS* (n=449)		NPSS** (n=1874)		p
Age, years, n (%)					
20–24	177	(39.4)	537	(28.7)	<0.0001
25–29	165	(36.7)	600	(32.0)	0.0629
30–34	107	(23.8)	737	(39.3)	<0.0001
Race/ethnicity, n (%)					
Hispanic	208	(46.3)	598	(31.9)	<0.0001
Black	79	(17.6)	279	(14.9)	0.1664
White	137	(30.5)	828	(44.2)	<0.0001
Other	25	(6.0)	169	(9.0)	0.0177
Health insurance, n (%)					
Private	165	(36.7)	677	(36.1)	0.8479
Medicaid	231	(51.4)	486	(25.9)	<0.0001
Self-pay	36	(8.0)	507	(27.1)	<0.0001
Other	17	(3.8)	204	(10.9)	<0.0001
Poverty level					
Poverty level ≥20%#	122	(27.2%)	356	(19.0)	0.0002
Median (IQR) [%]##	11.4	(6–21.1)	11	(5.8–18.5)	0.0302

\* PASS – pregnancy-associated severe sepsis; \*\* NPSS – severe sepsis not associated with pregnancy; # Percent of severe sepsis hospitalizations living at zip code areas where the level of poverty was 20% or higher; ## Percent of people living below poverty level at the zip code of residence of severe sepsis hospitalizations.

number and type of organ failures for both groups are detailed in Tables 1 and 2.

Obesity was reported in 16 (3.6%) and 127 (6.8) PASS and NPSS hospitalizations, respectively (p=0.0149). The majority of PASS (85%) and NPSS (83%) hospitalizations were admitted to the ICU.

The genital tract was the most common reported site of infection among women with PASS, while infection of the urinary tract was the most common reported among those with NPSS. More than 1 site of infection was reported in 152 (33.9%) and 371 (19.8%) hospitalizations with PASS and NPSS, respectively. A site of infection was not reported in 125 (27.8%) and 443 (23.6%) hospitalizations with PASS and NPSS, respectively.

The number of failing organs was lower among PASS hospitalizations and the rate of those with 3 or more failing organs was nearly half that of women with NPSS. On subgroup analysis of severe sepsis hospitalizations with the respiratory tract reported

as the only site of infection (58 and 350 hospitalizations among PASS and NPSS, respectively), the number of organ failures and the number of those with ≥3 organ failures was lower among PASS vs. NPSS hospitalizations: 2 (1–2) vs. 2 (1–3) [p=0.0038] and 8 (13.8%) vs. 128 (36.6%) [p=0.0011], respectively.

Organ failures most commonly included the respiratory and cardiovascular systems, each affecting, although statistically different for cardiovascular failure, nearly half of severe sepsis hospitalizations in each group. Mechanical ventilation was used less often among women with respiratory failure and PASS than among those with NPSS (152/244 [62.3%] vs. 663/931 [71.2]; p=0.0090, respectively). Although hemodialysis was used at a lower rate among PASS hospitalizations with acute renal failure vs. those with NPSS, the difference was not statistically significant (9/82 [11.0%] vs. 92/607 [15.2%]; p=0.4018, respectively).

Comparative data on crude hospital mortality for the whole cohort and examined subgroups are detailed in Table 3. Crude

**Table 2.** Comparative features of sites of infection, rates of ICU admission, and organ failure among severely septic women with and without pregnancy-associated hospitalizations.

Variable	PASS* (n=449)		NPSS** (n=1874)		p
Sites of infection, n (%)#					
Respiratory	102	(22.7)	629	(33.6)	<0.0001
Urinary	152	(33.9)	750	(40.0)	0.0185
Genital	200	(44.5)	3	(0.2)	<0.0001
Abdominal	37	(8.2)	260	(13.9)	0.0017
Endocarditis	1	(0.2)	33	(1.8)	0.0265
Skin and soft tissue	1	(0.2)	21	(1.1)	0.1354
Device-related	13	(2.9)	143	(7.6)	0.0005
Other###	6	(1.3)	58	(3.1)	0.0595
Admission to ICU, n (%)	382	(85.1)	1555	(83)	0.3157
Number of failing organs					
(median [IQR])	1	(1–2)	2	(1–3)	0.0005
≥3 Organ failures, n (%)	74	(16.5)	503	(26.8)	<0.0001
Type of organ failure###, n (%)					
Respiratory	244	(54.3)	931	(49.7)	0.0850
Cardiovascular	220	(49.0)	1025	(54.7)	0.0339
Renal	82	(18.3)	607	(32.4)	<0.0001
Hematological	99	(22.0)	441	(23.5)	0.5444
Metabolic	83	(18.5)	369	(19.7)	0.6080
Neurological	11	(2.4)	166	(8.9)	<0.0001

\* PASS – pregnancy-associated severe sepsis; \*\* NPSS – severe sepsis not associated with pregnancy; # The total rates exceed 100% due to presence of more than one site of infection among severe sepsis hospitalizations; ### Other infections included bloodstream (3) and central nervous system (3) for PASS, and bloodstream (20) and central nervous system (39) for NPSS; #### No hepatic failure was reported in either group.

**Table 3.** Comparative hospital mortality (n [%]) among severely septic women with and without pregnancy-associated hospitalizations for the whole cohort and selected subgroups.

Variable	PASS*		NPSS**		p
All	30/449	(6.7)	265/1874	(14.1)	<0.0001
≥3 Organ failures	13/74	(17.6)	167/503	(33.2)	0.0100
Respiratory tract infection	3/58	(5.2)	71/350	(20.0)	0.0098

\* PASS – pregnancy-associated severe sepsis; \*\* NPSS – severe sepsis not associated with pregnancy; # Severe sepsis hospitalizations (among the whole cohort) with reported 3 or more organ failures; ## Severe sepsis hospitalizations with reported infection of the respiratory tract as the only site of infection.



hospital mortality was consistently lower among PASS hospitalizations for the whole cohort and the subgroups. The adjusted odds ratios (95% CI) of hospital mortality among PASS hospitalizations for the whole cohort and those with  $\geq 3$  organ failures were 0.57 ([0.38–0.86];  $p=0.007$ ) and 0.44 ([0.23–0.85];  $p=0.0114$ ), respectively.

## Discussion

We unexpectedly found that both crude and adjusted hospital mortality were markedly lower among women with PASS when compared with contemporaneous women with NPSS, although the comparison was for the same age range and after exclusion of those with reported chronic comorbidities. Lower mortality among women with PASS was observed consistently across examined subgroups with multiple failing organs and among those with isolated infection of the respiratory tract.

Multiple studies have demonstrated consistently lower mortality among women with PASS [4,7] as compared to that reported in studies of severely septic patients in the general population [8,9]. However, no directly comparative studies have been reported, to the best of our knowledge, on mortality of PASS vs. NPSS, nor on outcomes of severe sepsis among young and otherwise healthy adults. A key barrier to such comparative studies has been the lack, until the last few years, of studies focused specifically on PASS, and the rarity of severe sepsis in the obstetric population. These challenges make a population-level approach more suitable for comparative outcome studies.

The predominance of genital tract infections vs. that of urinary and respiratory tract infections among PASS and NPSS hospitalizations in the present study is in agreement with prior reports [7,23]. There have been no studies on the distribution of sites of infections specifically among young and otherwise healthy women with severe sepsis not associated with pregnancy.

More than 1 site of infection was often reported in both groups and similar findings were noted in prior reports on septic shock [24] and ICU-managed necrotizing fasciitis [25]. No site of infection was reported in about 1 in 4 severe sepsis hospitalizations in both PASS and NPSS groups, a similar rate compared to that in prior studies of PASS [7] and septic shock in the general population [24].

The severity of illness, as reflected by the number of organ failures, was lower among PASS hospitalizations for the whole cohort and in the subgroup examination of those with isolated respiratory tract infection. Although not conclusive, the finding of lower crude and adjusted mortality among PASS

hospitalizations with 3 or more failing organs further supports the possibility that individual organ failures may have been less severe in women with PASS as compared to those with NPSS.

While both crude and adjusted hospital mortality was consistently lower among PASS vs. NPSS hospitalizations, possible residual imbalances between group attributes may have contributed to the observed difference. It is possible that some of the examined chronic comorbidities may have been unreported in some hospitalizations. However, there are no studies to suggest that such underreporting in administrative data is more common among non-obstetric patients.

The marked imbalance in infection sites with the predominance of genital tract infections among PASS hospitalizations could have been a key factor contributing to the observed lower mortality in this group. However, hospital mortality was also nearly 4-fold lower among PASS hospitalizations with isolated respiratory tract infection as compared to the corresponding NPSS subgroup. Finally, in a recent population-based study of PASS, genital tract infection was not a predictor of lower hospital mortality [4]. Because we could not obtain adequate microbiology data from the administrative data set, the higher mortality among NPSS hospitalizations could be attributed in part to higher frequency of more virulent or opportunistic pathogens. However, there are no data to support this hypothesis for severe sepsis among young and otherwise healthy women as compared to their obstetric counterparts. Similarly, antimicrobial resistance patterns of isolated microorganisms are not reported in administrative data. There may have been higher frequency of severe sepsis due to hospital- or healthcare-associated infections and a possibly corresponding higher rate of initially inappropriate antimicrobial therapy in the NPSS group, which could have contributed to their higher hospital mortality. However, obstetric patients are as likely or more likely to have severe sepsis due to drug-resistant pathogens than their age-similar non-obstetric counterparts, due to the more common exposure of the former to invasive procedures and common occurrence of severe sepsis as hospital-acquired or healthcare-associated events [26].

Finally, administrative data sets do not include information on the timeliness and appropriateness of care of severe sepsis. Thus, the observed higher hospital mortality in the NPSS group may have been in part due to delayed recognition and inadequate time-sensitive interventions [27] in these women as compared to the PASS group. In addition, although admission rates to the ICU were similar and near-universal in both groups, timeliness of transfer to the ICU and subsequent critical care may have been less adequate in the NPSS group. However, although inadequate initial care of severe sepsis remains common in the general population [28], there are well-described unique challenges for early recognition and timely intervention among women with PASS. These are related to in

part to an overlap between some of the early manifestations of sepsis and those of normal pregnancy [26]. There is well-documented evidence of highly prevalent substandard care related to delayed recognition of severe sepsis and delayed or inappropriate emergent interventions and overall escalation of care in women with PASS [5,6,29]. Moreover, the rarity of PASS further contributes to the lack of adequate familiarity and development of expertise by frontline clinicians. To illustrate this latter challenge, the annual number of PASS hospitalizations in Texas, using the highest reported estimate of about 50 per 100 000 births [7] and with about 400 000 annual births in the state [30], would be about 200 per year. This means that most hospitals and the majority of frontline clinicians in the state will not see a single PASS patient in a given year, as compared to many non-obstetric severely septic patients [31]. Thus, it is unlikely that substantially better care of severe sepsis occurred among the PASS group in the present cohort.

The number of organ failures and severity of individual failing organs are among the key determinants of mortality among severely ill patients in general [32] and in those with severe sepsis [8]. The contemporary concept of sepsis and, specifically, severe sepsis is framed around the patient's systemic response to infection [33,34], as aptly observed by Lewis Thomas, stating that "microorganisms... turn out... to be rather bystanders... It is our response to their presence that makes the disease" [35]. It is thus likely that the lower severity of illness has contributed to the markedly lower mortality observed consistently for the whole cohort and the exploratory subgroups of women with PASS, as compared to their non-obstetric counterparts. However, our study was not designed to determine the underlying mechanisms of the observed lower hospital mortality among PASS hospitalizations, and with the present study design we cannot exclude other unaccounted-for confounders to explain the observed lower number of failing organ and apparent lower severity of some of the individual failing organs.

Nevertheless, given the aforementioned findings, it can be hypothesized that the apparent lower severity of illness among women with PASS represents an intrinsic difference between obstetric and non-obstetric patients in their response to infection. The observed organ damage and resultant failure among patients with severe sepsis represents the impact of dysregulated response to infection [36]. Although these responses to infection were studied extensively among severely septic patients in the general population, the corresponding gene activation patterns and related downstream cellular response cascades, such as those involving the innate and adaptive immune systems, remain largely unexplored among obstetric severely septic women. Indeed, pregnant women were systematically excluded from studies exploring gene activation and downstream biomarker signature patterns of sepsis [37], and possibly were not considered as a separate subgroup in others [38]. Thus, the

results of the present study warrant further exploration into the infection-related molecular response patterns among women with PASS, with a potential, if confirmed, to inform clinical care of severe sepsis in both obstetric and non-obstetric patients.

The present study has several limitations. We used a retrospective study design and an administrative data set, with their known limitations. However, the rarity of PASS constrains traditional clinical study approaches to comparative investigations. In addition, TIPUDF does not allow identification of individual patients and thus cannot account for possible multiple severe sepsis hospitalizations of the same patient. However, a similar approach was used in other population-level investigations of severe sepsis [3,8,9]. In addition, multiple hospitalizations for severe sepsis by a given patient are not likely to explain the observed magnitude of the differences in hospital mortality in the present study or, importantly, the consistently lower mortality among women with PASS in prior non-comparative studies using a different design [7,39].

We distinguished between PASS and NPSS groups by first using ICD-9-CM codes to identify pregnancy-associated hospitalizations; it is possible that some severe sepsis hospitalizations may have been misclassified between pregnancy-associated vs. those not associated with pregnancy. However, hospitalizations associated with pregnancy were the most commonly reported category of hospitalization in Texas [40], and thus can be expected to have a high level of familiarity among clinicians and coders. In addition, a similar approach has been used by other investigators to identify morbidity and mortality events associated with pregnancy among hospitalized women when using administrative data sets [41,42].

The most accurate approach to identify severe sepsis in administrative data is uncertain. A recent study of national data by Gaieski et al. found a 3.5-fold difference in the number of identified severe sepsis hospitalizations among 4 ICD code-based methods, although all trended comparably over time [43]. We used a conservative approach to identify severe sepsis hospitalizations, which was reported to result in estimates of burden of disease comparable to concurrent chart-based review [44]. Also importantly, a specific approach to identify hospitalizations with severe sepsis would not explain the marked differences in outcome observed between the PASS and NPSS groups.

Although our approach to identify sites of infection is similar to that of prior reports [20,45], it is possible that the sites of infection in some severe sepsis hospitalizations have been misclassified or not reported as a result of using administrative data. However, it is unlikely that this has occurred in a substantially imbalanced manner between the PASS and NPSS groups, and the distribution of key identified sites of infection in our study is comparable to that in prior reports [3,23].

In addition, established severity-of-illness scores cannot be derived from administrative data and we used the number of failing organs as a surrogate measure. However, a similar approach was employed by other investigators [8], and the number of failing organs was associated with incremental risk of death among PASS hospitalizations [4] and in the general population with severe sepsis [46,47].

Finally, although we examined severe sepsis in a large state with a diverse population, the characteristics of PASS and NPSS may vary across states and nationally. Further studies are needed in other populations in both developed and developing countries.

## Conclusions

The present study describes, to the best of our knowledge, the first comparison of mortality between women with severe sepsis associated vs. that not associated with pregnancy in a contemporaneous cohort, with similar age range and following exclusion of women with reported chronic comorbidities.

In this pragmatic comparative study, hospital mortality was unexpectedly lower among PASS hospitalizations as compared to

those with NPSS, despite the contemporary challenges for early recognition and timely effective intervention among the former. The severity of illness appears to be lower among women with PASS and was likely a key contributor to their lower mortality.

Our findings demonstrate that previous reports of lower mortality in women with PASS, as compared to that of that in the general population, cannot be readily explained by the younger age of the former, their lack of or lower burden of chronic illness, or by the predominance of genital tract infections in obstetric patients.

Further studies in other populations are warranted to corroborate our findings. Future investigations into the gene activation patterns and downstream cellular and molecular responses to infection among women with PASS may inform clinicians about the impact of pregnancy on outcomes of severely septic patients and possible sources of the observed outcome differences as compared with their non-obstetric counterparts.

## Acknowledgment

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**Supplementary Table 1.** International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) codes for identifying pregnancy-related hospitalization (where only 3 or 4-digit codes are listed, all associated subcodes are included).

Category	ICD-9-CM codes
Pregnancy with abortive outcome	630–639.9
Complications mainly related to pregnancy	640–648.9
Normal delivery and other indications for care in pregnancy labor and delivery	650–659.9
Complications occurring during mainly the course of labor and delivery	660–666.9
Complications of the puerperium	670–676.9
Outcome of delivery	V27.0–V27.9

**Supplementary Table 2.** International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) codes for identifying bacterial and fungal infectious process (where only 3 or 4-digit codes are listed, all associated subcodes are included).

Category	ICD-9-CM codes
Salmonella septicemia	003.1
Septicemic plague	020.2
Anthrax septicemia	022.3
Meningococcal septicemia	036.2
Waterhouse-Friderichsen syndrome	036.3
Septicemia	038
Herpetic septicemia	054.5
Gonococemia	098.89
Disseminated candidal infection	112.5



**Supplementary Table 3.** International Classification of Diseases, Ninth Edition, Clinical Modification codes for classification of organ failure (where only 3 or 4-digit codes are listed, all associated subcodes are included).

Category	ICD-9-CM codes
Respiratory	
Acute respiratory failure	518.81
Other pulmonary insufficiency, not elsewhere specified (includes acute respiratory distress, acute respiratory insufficiency, acute respiratory distress syndrome)	518.82
Pulmonary insufficiency following trauma, or surgery	518.5
Acute and chronic respiratory failure	518.84
Respiratory abnormalities, not otherwise specified	786.09
Respiratory arrest	799.1
Invasive mechanical ventilation	96.7–96.72
Cardiovascular	
Hypotension, not otherwise specified	458.8, 458.9
Shock during or following labor and delivery	669.1
Shock, not otherwise specified	785.50
Cardiogenic shock	785.51
Other shock without mention of trauma	785.59
Renal	
Acute renal failure 584	
Hepatic	
Acute necrosis of liver	570
Hepatic encephalopathy	572.2
Hepatic infarction	573.4
Hematologic	
Defibrination syndrome	286.6
Acquired coagulation factor deficiency	286.7
Coagulopathy (Other unspecified coagulation defects)	286.9
Thrombocytopenia (secondary or unspecified)	287.4, 287.5
Metabolic	
Acidosis (metabolic or lactic)	276.2
Neurologic	
Acute and subacute delirium	293.0, 293.1
Anoxic brain damage	348.1
Encephalopathy, not elsewhere classified	348.3
Coma	780.01
Other alteration of consciousness	780.09

**Supplementary Table 4.** International Classification of Diseases, Ninth Edition, Clinical Modification (ICD 9 -CM) codes for sites of infection (where only 3 or 4-digit codes are listed, all associated subcodes are included).

Category	ICD-9-CM codes
Respiratory	481-486, 510, 513
Blood	790.7, 572.1, 673.3
Endocarditis	112.81, 421
Central nervous system	320, 322, 324, 325
Gastrointestinal/abdominal	003, 008, 540-542, 530.4, 530.86, 562.01, 562.03, 562.11, 562.13, 566, 567, 569.5, 569.83, 572.0, 575.0, 531.1, 531.2, 531.5, 531.6 532.1, 532.2, 532.5, 532.6, 533.1, 533.2, 533.5, 533.6, 534.1, 534.2, 534.5, 534.6
Urinary	590, 599.0
Genital	615, 634.0, 635.0, 636.0, 637.0, 638.0, 639.0, 646.6 658.4
Skin and soft tissue	675.1, 680, 682, 686, 998.5
Bone and joint	711.0, 730
Device-related	996.6

**Supplementary Table 5.** International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) codes for selected life-support interventions.

Category	ICD-9-CM codes
Mechanical ventilation	96.70–96.72
Hemodialysis	38.95

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