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The Effect of Staphylococcal Cassette Chromosome *mec* (SCC*mec*) Type on Clinical Outcomes in Methicillin-Resistant *Staphylococcus aureus* Bacteremia

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Abstract

Objectives—The impact of staphylococcal cassette chromosome *mec* (SCC*mec*) type on mortality in methicillin-resistant *Staphylococcus aureus* (MRSA) infections remains unclear. The objective of this study was to determine the association between SCC*mec* type and mortality in MRSA bacteremia.

Methods—A cohort study of patients who were hospitalized with MRSA bacteremia was conducted within a university health system. A multivariable logistic regression model was developed to evaluate the association of SCC*mec* type with 30-day in-hospital mortality.

Results—Thirty-four of a total of 184 patients with MRSA bacteremia died, resulting in a mortality rate of 18.5%. Adjusted risk factors for 30-day mortality included APRDRG Risk of Mortality score (odds ratio [OR], 5.33; 95% confidence interval [CI], 2.28-12.4; $P < 0.001$), white blood cell count (OR, 1.09; 95% CI, 1.03-1.15; $P = 0.002$), and malignancy (OR, 3.25; 95% CI, 1.17-9.02; $P = 0.02$). On multivariable analyses, SCC*mec* II was not significantly associated with mortality in patients with MRSA bacteremia (OR, 1.85; 95% CI, 0.69-4.92; $P = 0.22$).

Conclusions—Mortality in MRSA bacteremia was independent of SCC*mec* type. SCC*mec* type II is most likely a marker for disease severity rather than a direct mediator of mortality. Further research is needed to elucidate the factors associated with poor clinical outcomes in MRSA infections.

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Keywords

methicillin-resistant; *Staphylococcus aureus*; outcomes; bacteremia

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most common causes of healthcare-associated infections worldwide and is associated with significant morbidity and mortality.¹ Methicillin resistance is mediated by acquisition of the *mecA* gene, which is located within the staphylococcal cassette chromosome *mec* (SCC*mec*) element.² In recent years, MRSA has also emerged as an important cause of infections in the community setting.³ Despite the lack of a uniform definition of community-associated MRSA (CA-MRSA) in the literature, the term has usually been used to describe strains causing infections in patients without recent contact with the healthcare environment.³ However, recent epidemiologic evidence indicates that CA-MRSA strains are increasingly causes of nosocomial infections,⁴ and that traditional epidemiologic definitions and risk factors may no longer reliably differentiate between CA-MRSA and healthcare-associated MRSA (HA-MRSA).⁵

From a molecular standpoint, CA-MRSA has typically been distinguished from HA-MRSA by the SCC*mec* element, with SCC*mec* IV and V predominating in CA-MRSA strains and SCC*mec* I, II, and III in HA-MRSA strains.³ Despite the increasing spread of CA-MRSA into the hospital setting, the impact of SCC*mec* type on mortality in MRSA infections remains unclear. Studies to date evaluating this association have demonstrated conflicting results, most likely due to differences in patient populations, geographic region (e.g., United States, Asia), anatomic site of infection, selection of reference groups, and lack of multivariable analyses.⁶⁻¹⁴ Furthermore, only a proportion of these studies have focused specifically on bacteremia,^{6, 8, 12-14} a major source of healthcare-associated infections due to MRSA and one associated with significant morbidity and mortality.¹⁵ These studies have also demonstrated conflicting results, and the majority evaluated patient populations outside of the United States^{6, 12, 14} where different SCC*mec* types predominate.

We conducted this cohort study to determine the association between SCC*mec* type and mortality in MRSA bacteremia. Specifically, we compared mortality in patients with *S. aureus* bacteremia with SCC*mec* II as opposed to SCC*mec* IV, the predominant SCC*mec* types in the United States.⁴

Patients and Methods

Study design and setting

This retrospective cohort study was conducted at two hospitals in the University of Pennsylvania Health System (UPHS) in Philadelphia: the Hospital of the University of Pennsylvania (HUP), a 725-bed academic tertiary care medical center, and Penn Presbyterian Medical Center (PPMC), a 344-bed urban community hospital. The study was approved by the institutional review board of the University of Pennsylvania.

Study population

All hospitalized patients with an episode of MRSA bacteremia occurring between 1 December 2007 and 31 May 2009 were identified through the HUP Clinical Microbiology Laboratory, which processes all specimens obtained from patients at HUP and PPMC. All of

these patients were subsequently included in the study. For patients with multiple blood cultures positive for MRSA, only the first culture was included for analysis.

Microbiologic methods

Identification and susceptibility testing of *S. aureus* was performed and interpreted according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Standard susceptibility testing was performed using Vitek2. SCCmec typing was performed as previously described.¹⁶ The vancomycin minimum inhibitory concentration (MIC) of all isolates was determined by the Etest using Mueller-Hinton agar (BBL, BD Diagnostic Systems, Franklin Lakes, NJ, USA)¹⁷ with reduced vancomycin susceptibility defined as an Etest vancomycin MIC >1.0 µg/ml.^{18, 19} Vancomycin hetero-resistance was screened for using the macro-Etest method using Etest GRD vancomycin/teicoplanin strips with brain heart infusion agar¹⁷ and by growth on vancomycin-containing brain heart infusion agar;²⁰ a positive result for either screening test was confirmed by population analysis using a Spiral Plater (Advanced Instruments, Norwood, MA, USA) and inoculation onto vancomycin brain heart infusion agar (BBL).²¹ Detection of the genes encoding Panton-Valentine leukocidin (PVL) was performed using real-time polymerase chain reaction using previously described methods.²² Isolates were evaluated for accessory gene regulator (*agr*) dysfunction via delta-hemolysin production using a beta-hemolysin disk.²³

Data collection

Data were abstracted from the Pennsylvania Integrated Clinical and Administrative Research Database (PICARD),^{24, 25} which includes demographic, laboratory, pharmacy, and billing information. The following data were collected for all patients: baseline demographics, origin at the time of hospital admission (i.e., physician referral, transfer from another facility, or admission through the Emergency Department), previous admission to UPHS in the 30 days prior to the culture date, hospital location at the time of infection (i.e., intensive care unit [ICU] or medical floor), nosocomial infection (date of the culture 48 hours after admission), white blood cell count (WBC) on the culture date, and All Patient Refined-Diagnosis Related Group (APRDRG) Risk of Mortality and Severity of Illness scores.²⁶ Infections were classified as healthcare-associated if the date of the first positive blood culture was 48 hours from the date of admission, or if the patient had been previously hospitalized at HUP or PPMC in the 30 days prior to the culture date or was admitted as a transfer from another institution. Otherwise, infections were classified as community-onset. Data on the following conditions was collected in relation to the positive blood culture date: diabetes mellitus, HIV infection, malignancy, renal insufficiency (creatinine 2.0 mg/dL or the requirement of dialysis), solid organ or hematopoietic stem cell transplantation, neutropenia (absolute neutrophil count <500/mm³), and receipt of an immunosuppressive agent (e.g., corticosteroids, tacrolimus) in the prior 30 days. The Charlson comorbidity index was calculated for each subject.²⁷ Chart review was performed to collect data on the presence of complicated infection (i.e., endocarditis, osteomyelitis, septic arthritis, epidural and/or spinal abscess) and the presence of intravascular devices (i.e., intravascular catheter, pacemaker or defibrillator, arteriovenous fistula or graft) prior to the episode of bacteremia.

Information on all antimicrobial therapy administered during the same hospitalization was collected, including the time of receipt in relation to the culture date. Antibiotics were considered to be appropriate in relation to treatment of the episode of MRSA bacteremia if they were determined to be active *in vitro* against the isolate via standard susceptibility testing. The primary outcome was crude in-hospital 30-day mortality, defined as death in the hospital from any cause occurring in the 30 days after the date of the first positive blood culture.

Statistical analysis

Continuous variables were compared using the Student's t-test or Wilcoxon rank-sum test and categorical variables were compared using the χ^2 or Fisher's exact test. Bivariable analyses were performed to determine the association between SCCmec type and 30-day in-hospital mortality, with the primary exposure of interest being SCCmec type II. Stratified analyses were conducted to elucidate where confounding and interaction were likely to exist in multivariable analyses, using the Mantel-Haenszel test for summary statistics.²⁸ In particular, location in the ICU, hospital of admission, and healthcare-associated infection were designated *a priori* as potential effect modifiers of interest. Effect modification was assumed to be present when the test for heterogeneity between the odds ratios (ORs) for different strata yielded a *P* value <0.05. The Mantel-Haenszel test for summary statistics²⁸ was used to evaluate the effects of each variable of interest as a possible confounder. Adjusted ORs with 95% confidence intervals (CI) were calculated using multiple logistic regression for the outcome of 30-day in-hospital mortality. A stepwise selection procedure was used for all multivariable analyses, with variables with *P* values <0.20 on bivariable analyses or noted to be confounders on stratified analyses considered as candidate variables and maintained in the final model if their inclusion resulted in a 15% change in the effect measure for the primary association of interest or were statistically significant on likelihood ratio testing.²⁹

For all calculations, a 2-tailed *P* value <0.05 was considered to be significant. All statistical calculations were performed using commercially available software (STATA version 11.0; StataCorp LP, College Station, Texas, USA).

Results

Study population

A total of 184 unique patients with MRSA bacteremia were identified during the study period. The distribution of SCCmec type among isolates was as follows: 109 (59.2%) with SCCmec II and 75 (40.8%) with SCCmec IV. Baseline clinical and demographic characteristics of patients with MRSA bacteremia are shown in Table 1. Patients with bacteremia due to MRSA harboring SCCmec II compared to SCCmec IV were older (mean age 62.8 and 55.1 years, respectively; *P*=0.002), had a higher APRDRG Risk of Mortality score at the time of MRSA isolation (mean 2.6 and 1.8, respectively; *P*=0.004), and had a significantly longer length of stay prior to the culture date (11.1 and 2.49 mean days, respectively, *P*=0.02).

Microbiologic characteristics

Isolates with SCCmec II versus SCCmec IV were more likely to be characterized by reduced vancomycin susceptibility (51.4% and 22.7%, respectively; *P*<0.001)³⁰ and less likely to be PVL positive (0.9% and 68.0%, respectively, *P*<0.001). There were no significant differences in the proportion of isolates with SCCmec II and SCCmec IV that were characterized by vancomycin hetero-resistance (6.4% and 2.7%, respectively; *P*=0.36) or *agr* dysfunction (16.5% and 10.7%, respectively; *P*=0.29).

In regard to antimicrobial susceptibility rates, MRSA isolates with SCCmec IV compared to those with SCCmec II demonstrated significantly higher rates of susceptibility to clindamycin (86.7% and 4.6%, respectively; *P*<0.001) and levofloxacin (41.3% and 0.92%, respectively; *P*<0.001). However, there were no significant differences in susceptibility rates for isolates with SCCmec IV versus SCCmec II for tetracycline (94.7% and 98.2%, respectively; *P*=0.23) and trimethoprim-sulfamethoxazole (94.7% and 99.1%, respectively; *P*=0.16).

Risk factors for 30-day in-hospital mortality

A total of 34 patients died while hospitalized for MRSA bacteremia, resulting in a crude mortality rate of 18.5%. The mortality rate was 23.9% and 10.7% for patients with MRSA isolates characterized by *SCCmec* II and *SCCmec* IV, respectively ($P=0.03$). Results of bivariable analyses of risk factors associated with in-hospital mortality are given in Table 2. The majority of patients received appropriate antibiotics, specifically 99.3% of patients who survived and 96.9% of patients who died during hospitalization, with vancomycin the most commonly administered initial antibiotic (86.7% and 91.2%, respectively; $P=0.58$).

On multivariable analyses of risk factors for 30-day in-hospital mortality (Table 3), there was no significant effect modification by location in the ICU ($P=0.26$), hospital of admission ($P=0.21$), or healthcare-associated infection ($P=0.16$). The unadjusted OR between *SCCmec* II and mortality was 2.62 (95% CI 1.06-7.12, $P=0.03$). On multivariable analyses, independent risk factors for in-hospital mortality included APRDRG Risk of Mortality score (OR 5.33, 95% CI 2.28-12.4, $P<0.001$), malignancy (OR 3.25, 95% CI 1.17-9.02, $P=0.02$), and WBC count on the culture date (OR 1.09, 95% CI 1.03-1.15, $P=0.002$). After controlling for confounders, *SCCmec* II was not significantly associated with greater 30-day in-hospital mortality (OR 1.85, 95% CI 0.69-4.92, $P=0.22$).

Discussion

In this cohort study of patients with MRSA bacteremia, we found that *SCCmec* type, specifically *SCCmec* II compared to *SCCmec* IV, was not significantly associated with mortality. Furthermore, isolates harboring *SCCmec* IV had higher susceptibility rates to clindamycin and levofloxacin compared to those with *SCCmec* II. The results of our study also demonstrated that a higher standardized mortality risk score, the presence of malignancy, and a higher white blood cell count were independent risk factors for mortality in MRSA bacteremia.

Previous studies have demonstrated conflicting results in regard to the role of *SCCmec* type on mortality in infections due to MRSA.⁶⁻¹⁴ In a study evaluating patients with MRSA skin and soft tissue infections,¹¹ *SCCmec* II was associated with greater mortality compared to both MRSA with other *SCCmec* types (primarily IVa) and methicillin-susceptible *S. aureus* (MSSA). In a larger study of 465 MRSA isolates responsible for skin and soft tissue infections from a phase IV clinical trial,¹⁰ clinical and microbiologic outcomes, including mortality, were independent of *SCCmec* type. A study evaluating 100 community-associated MRSA isolates from various sources (e.g., respiratory tract, bacteremia) demonstrated greater mortality in the *SCCmec* II/III group compared to the *SCCmec* IV group (i.e., two patients and one patient died during hospitalization, respectively), although there was no difference in clinical or microbiologic success rates.⁷ However, all of these studies were limited to bivariable analyses. Finally, a study evaluating clinical outcomes in MRSA pneumonia⁹ found that *SCCmec* II was associated with increased mortality on bivariable analysis; however, this association was not significant on subsequent multivariable analyses.

Studies evaluating the impact of *SCCmec* type on mortality exclusively in MRSA bacteremia,^{6, 8, 12-14} as was the focus of our study, have also demonstrated conflicting results, as well as significant heterogeneity in regard to patient population, ascertainment of potential confounders, geographic region, and use of multivariable analyses. A few studies^{6, 8} have found increased mortality with MRSA strains harboring *SCCmec* II, but these were limited by comparison to MSSA only,⁶ failure to account for time to receipt of appropriate antimicrobial therapy,⁸ and evaluation of only community-onset infections.⁶ Other studies¹²⁻¹⁴ have demonstrated no association between *SCCmec* type and mortality, although these were limited by use of bivariable analyses only,¹² or evaluated a patient

population from a different geographic region than the present study (i.e., Asia versus the United States)^{12, 14} where different *SCCmec* types predominate. Our study demonstrated no association between *SCCmec* II and mortality, and to our knowledge, is the largest to date evaluating the impact of *SCCmec* type on mortality in MRSA bacteremia using multivariable analyses. The results are further strengthened by the comprehensive capture of potential confounders, including time to receipt of appropriate antimicrobial therapy, standardized severity of illness and risk scores, and presence and/or removal of intravascular devices.

Factors that are likely to contribute to the relationship between MRSA infection and mortality include bacterial virulence and fitness, host factors including comorbidities and severity of illness, and the receipt of early and appropriate antimicrobial therapy.³¹ It is possible that *SCCmec* II may be a marker of illness severity and/or greater exposure to the healthcare system rather than a direct mediator of mortality, and indeed, in our study and others,^{4, 7, 14} *SCCmec* II compared to *SCCmec* IV was associated with significantly higher standardized severity of illness scores and longer hospital lengths of stay prior to isolation of MRSA. Therefore, in the hospitalized population, which is generally characterized by a greater severity of illness and the presence of more comorbidities compared to the community population, *SCCmec* II may not have a direct causal effect on mortality. Along these lines, in the present study, while *SCCmec* II was a risk factor for mortality on bivariable analyses compared to *SCCmec* IV, after adjustment for potential confounders including a standardized score for mortality risk, there was no association between *SCCmec* type and mortality.

The receipt of appropriate antimicrobial therapy (e.g., one or more agents that are active *in vitro* against the isolate), as well as timing of receipt, have been shown to decrease mortality in MRSA bacteremia.³² Notably, in our study, the majority of patients with bacteremia due to MRSA with both *SCCmec* II and *SCCmec* IV received appropriate antimicrobial therapy (98.7% and 99.1%, respectively; $P>0.99$). Furthermore, there was no significant difference in time to administration of appropriate antimicrobial therapy in patients with bacteremia due to MRSA with either *SCCmec* II or *SCCmec* IV (mean of 16.1 and 15.8 hours, respectively, $P=0.31$).

In regard to organism factors, evidence suggests that MRSA strains with *SCCmec* IV may exhibit enhanced virulence and/or fitness compared to those harboring *SCCmec* II.^{33, 34} Indeed, some studies have demonstrated an increased risk of metastatic infection with *SCCmec* IV,^{8, 13} although this did not translate to an increased risk of persistent bacteremia.¹³ Interestingly, *SCCmec* II was associated with elevated vancomycin MIC in our study,³⁰ although this did not increase mortality in the final multivariable model.

There are several potential limitations of our study. We were unable to ascertain pharmacologic data on therapeutic drug monitoring in patients receiving vancomycin. Selection bias is a potential concern; however, patients with MRSA bacteremia were identified through the Clinical Microbiology Laboratory which processed and cultured all specimens obtained at HUP and PPMC during the study period, thereby minimizing the likelihood of excluding potential microbiologic isolates. Finally, the present study was conducted in a single healthcare system, and these results may not be generalizable to other institutions or geographic locations.

In conclusion, we found that after adjustment for relevant confounders, mortality in MRSA bacteremia is independent of *SCCmec* type. It is clear that the epidemiology of MRSA is complex and evolving, and strains possessing *SCCmec* IV are an increasing cause of infections in the nosocomial setting, including invasive infections such as bacteremia.

Further research is needed to elucidate potentially modifiable host and organism factors associated with mortality in MRSA infections.

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Table 1
Clinical and demographic characteristics of patients with methicillin-resistant *Staphylococcus aureus* bacteremia

Characteristic	SCCmec II ^a (n=109)	SCCmec IV ^a (n=75)	P Value
Age, mean years (SD)	63 (15.7)	55 (17.4)	0.002
Female sex	44 (40.4)	29 (38.7)	0.82
White race	71 (62.7)	35 (45.9)	0.07
HUP	85 (78.0)	43 (57.3)	0.003
Emergency Department admission	43 (39.5)	48 (64.0)	0.001
Nosocomial onset	38 (34.9)	12 (16.0)	0.007
Healthcare-associated	76 (69.7)	36 (48.0)	0.003
APRDRG Risk of Mortality score ^b , mean (SD)	2.3 (0.9)	1.8 (1.1)	0.004
HIV	2 (1.8)	7 (9.3)	0.03
Malignancy	32 (29.4)	13 (17.3)	0.06
Intravascular device	56 (51.4)	23 (30.7)	0.005
In-hospital length of stay prior to culture date, mean days (SD)	11.1 (52.9)	2.5 (8.8)	0.02
30-day in-hospital mortality	26 (23.9)	8 (10.7)	0.03

SD, standard deviation; HUP, Hospital of the University of Pennsylvania; APRDRG, All Patient Refined-Diagnosis Related Group.

^aData are presented as numbers (percentages) except where noted.

^bRisk of patient death as based on DRG. The four subclasses are numbered sequentially from 1 to 4 indicating respectively, minor, moderate, major, or extreme risk of mortality.

Table 2
Unadjusted risk factors associated with in-hospital mortality in methicillin-resistant *Staphylococcus aureus* bacteremia

Variable	No. (%) Survived (n=150) ^a	No. (%) Deceased (n=34) ^a	OR (95% CI) ^b	P Value
Age, mean years (SD)	58.7 (16.9)	64.1 (15.7)	N/A	0.10
Female sex	57 (38.0)	16 (47.1)	1.45 (0.63-3.28)	0.33
White race	87 (56.8)	19 (50.0)	0.64 (0.28-1.44)	0.26
PPMC admission	51 (34.0)	5 (14.7)	0.33 (0.10-0.95)	0.04
Physician referral on admission	27 (18.0)	3 (8.8)	0.44 (0.08-1.59)	0.30
Nosocomial infection	39 (26.0)	11 (32.4)	1.36 (0.55-3.23)	0.52
Total duration of bacteremia from culture date, mean days (SD)	3.5 (4.6)	3.6 (5.6)	N/A	0.52
Receipt of appropriate antibiotic(s)	147 (99.3)	31 (96.9)	0.21 (0.003-17.1)	0.33
Days to receipt of appropriate antibiotics, mean (SD)	0.70 (1.2)	0.48 (0.63)	N/A	0.60
APRDRG Risk of Mortality score ^c , mean (SD)	1.9 (1.0)	2.8 (0.54)	N/A	<0.001
APRDRG Severity of Illness score ^c , mean (SD)	2.4 (0.64)	2.9 (0.41)	N/A	<0.001
Charlson Comorbidity score, mean (SD)	4.4 (4.6)	4.1 (3.4)	N/A	0.97
Intravascular device	64 (42.7)	15 (44.1)	1.06 (0.46-2.39)	>0.99
Removal of intravascular device	47 (73.4)	12 (80.0)	1.45 (0.33-8.91)	0.75
Complicated infection	52 (34.7)	10 (29.4)	0.79 (0.31-1.86)	0.69
Diabetes mellitus	46 (30.7)	11 (32.4)	1.08 (0.44-2.54)	0.84
Malignancy	32 (21.3)	13 (38.2)	2.28 (0.94-5.38)	0.05
Renal insufficiency	42 (28.2)	13 (38.2)	1.58 (0.66-3.65)	0.30
Neutropenia	4 (11.8)	7 (4.7)	2.70 (0.54-11.4)	0.13
Transplant (solid organ or hematopoietic stem cell)	19 (12.7)	2 (5.9)	0.43 (0.05-1.95)	0.38
Receipt of any immunosuppression 30 days prior to the culture date	15 (10.0)	8 (23.5)	2.77 (0.91-7.79)	0.04
ICU location on culture date	31 (20.7)	15 (44.1)	3.03 (1.27-7.10)	0.01
WBC count, mean X 10 ⁹ /L (SD)	12.4 (7.8)	16.6 (12.0)	N/A	0.07
Reduced vancomycin susceptibility	61 (40.7)	12 (35.3)	0.80 (0.33-1.83)	0.56
hGISA	7 (4.7)	2 (5.9)	1.28 (0.12-7.13)	0.67
PVL	46 (30.7)	6 (17.7)	0.49 (0.15-1.31)	0.15
<i>agr</i> dysfunction	20 (13.3)	6 (17.7)	1.39 (0.42-4.03)	0.59

OR, odds ratio; CI, confidence interval; SD, standard deviation; N/A, not applicable; PPMC, Penn Presbyterian Medical Center; APRDRG, All Patient Refined-Diagnosis Related Group; ICU, intensive care unit; WBC, white blood cell count; hGISA, glycopeptide heterointermediate *Staphylococcus aureus*; PVL, Panton Valentine leukocidin; *agr*, accessory gene regulator.

^aData are presented as numbers (percentages) except where noted.

^bORs unavailable for continuous variables.

^cRisk of patient death and severity of illness as based on DRG. The four subclasses are numbered sequentially from 1 to 4 indicating respectively, minor, moderate, major, or extreme risk of mortality or severity of illness.

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Table 3
Final multivariable model of risk factors associated with in-hospital mortality in methicillin-resistant *Staphylococcus aureus* bacteremia

Variable	OR (95% CI)	P Value
APRDRG Risk of Mortality score ^a	5.33 (2.28-12.4)	<0.001
Malignancy	3.25 (1.17-9.02)	0.02
WBC count on culture date	1.09 (1.03-1.15)	0.002
SCC <i>mec</i> II	1.85 (0.69-4.92)	0.22
Neutropenia	4.52 (0.77-26.4)	0.09

OR, odds ratio; CI, confidence interval; APRDRG, All Patient Refined-Diagnosis Related Group; WBC, white blood cell count.

^aRisk of patient death based on DRG. The four subclasses are numbered sequentially from 1 to 4 indicating respectively, minor, moderate, major, or extreme risk of mortality.