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Optimal Duration for Continuation of Statin Therapy in Bacteremic Patients

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1 **Optimal Duration for Continuation of Statin Therapy in Bacteremic Patients**

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12
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27 **Abstract**

28 **Background:** Evidence suggests statins may improve survival in patients with bloodstream
29 infections. However, there is no consensus on optimal timing and duration of exposure.

30 **Objectives:** To quantify statin therapy duration associated with decreased mortality in
31 bacteremic statin users.

32 **Methods:** We conducted a case-control study using OptumClinformatics™ with matched
33 Premier hospital data (08/2009-03/2013). Cases who died during the hospitalization were
34 matched 1:1 to survivors on disease risk scores (DRS). Post-admission statin therapy duration
35 was evaluated in patients with at least 90 days of pre-admission continuous statin use.
36 Classification and regression tree (CART) analysis was conducted to identify the optimal
37 duration of statin continuation which provided the lowest inpatient mortality. Logistic regression
38 was used to calculate the odds of mortality.

39 **Results:** We included 58 DRS matched pairs of cases and controls: 47 patients (41%)
40 continued statin therapy during the hospital admission, 15 (32%) cases and 32 (68%) controls.
41 The CART analysis partitioned the continuation of statin therapy at ≥ 2 days, representing lower
42 mortality for patients that continued statins for 2 days or more, and higher mortality for patients
43 who did not continue or remained on statins for only 1 day. Inpatient mortality was 76% lower
44 among those with at least 2 days of continued statin use (odds ratio 0.24, 95% confidence
45 interval 0.11-0.55).

46 **Conclusions:** Among matched cases and controls with at least 90 days of baseline statin use
47 prior to the admission, the continuation of statins for at least 2 days after admission
48 demonstrated a survival benefit among bacteremic patients.

49

50 **Introduction**

51 Inpatient mortality among patients with bloodstream infections remains high (16.3%).¹
52 Evidence from observational research suggests that statins may improve survival in patients
53 with bacteremia²⁻⁵ and sepsis,⁶⁻⁸ including 14-day⁵, 15-day², 31-180 day,⁹ and all-cause hospital
54 mortality.^{3,7,5} While several studies have reported reduced mortality with statins in bacteremic
55 patients, statin duration and measurement of outcomes differ across these studies.³⁻⁵ As a
56 result, rates of survival vary, particularly as statin exposure varies.^{3,9} Additionally, several of
57 these studies have identified an increase in mortality after cessation of statin therapy.^{3,10} Since
58 the length of statin treatment time varies between studies, there is no consensus as to whether
59 statin therapy should be continued among patients presenting to the hospital with bacteremia,
60 and if so, what duration of statin continuation would provide the maximum advantage in terms of
61 clinical outcomes.

62
63 While several meta-analyses^{11,12} and observational^{3-5,9} studies observed protective
64 effects with statins in bacteremia, one meta-analysis¹³ did not observe improvements in clinical
65 outcomes with statin use. However, this meta-analysis was conducted among critically-ill
66 patients with severe sepsis, and some of the included studies only had short durations of statin
67 use.^{3,4,9} Other studies with shorter statin durations also did not demonstrate a statistically
68 significant association between statin use and mortality.^{9,13,14} A recent randomized controlled
69 trial (RCT) evaluating the potential benefits of continued statin therapy on inflammatory
70 parameters and sepsis among patients with pre-existing statin use¹⁵ did not find clinical benefits
71 with continuation. As such, there is a lack of consistent evidence regarding the appropriate
72 exposure duration needed for statins to provide the greatest protective effects in bacteremic
73 patients. The main objective of this study was to identify a duration of statin therapy continuation
74 which minimized inpatient mortality among bacteremic patients.

75

76

77 **Methods**

78 A case-control study design was used to estimate a time breakpoint in statin
79 continuation at which the highest clinical benefit would be seen in terms of survival (i.e., lowest
80 inpatient mortality). This study was conducted using de-identified OptumClinformatics™
81 database (OptumInsight, Eden Prairie, MN) with matched Premier hospital data (10/01/2009-
82 03/31/2013) among adult (≥ 18 years) patients with a primary diagnosis of bacteremia during a
83 hospital admission.

84

85 Adult patients with continuous enrollment for at least six months in the commercial
86 health plan prior to hospital admission were included. Patients were included if they were
87 hospitalized between 04/01/2010 and 03/31/2013 with a primary diagnosis of bacteremia or
88 septicemia (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-
89 CM] codes 003.1, 020.2, 022.3, 036.2, 038.0, 038.1, 038.10-038.12, 038.19, 038.2, 038.3,
90 038.40-038.44, 038.49, 038.8, 038.9, 054.5, 449, 771.81, 995.91, 995.92, 790.7)¹⁶ by any
91 causative organism. We excluded patients who, on the first three days after hospital admission,
92 did not receive a minimum of two successive days of at least one antibiotic therapy that would
93 be used to treat bacteremia.¹⁷⁻²⁰ The index date was defined as the date of the first hospital
94 admission during the study period, and subsequent hospital admissions were not considered for
95 the analysis. From this cohort, only patients with a minimum of 90 days of continuous statin use
96 in the 90 days prior to admission were selected for inclusion to capture prevalent and adherent
97 statin users (Figure 1). The Charlson comorbidity index and chronic comorbidities were
98 captured from ICD-9-CM codes in the six months prior to admission and during the index
99 admission.²¹

100

101 Cases included those who died during the admission. Controls were selected from
102 survivors of the same cohort of adult patients who had a primary diagnosis of bacteremia on
103 hospital admission and received antibiotic therapy. Controls were matched to cases on disease
104 risk scores (DRS).²² DRS is a confounder summary method, which can be used in case-control
105 studies to control for confounding by calculating the predicated probability of an outcome in the
106 absence of exposure.^{23,24} The stratified DRS is a retrospective balancing score and therefore it
107 works in a similar manner in case-control studies as the propensity score works in cohort
108 studies. While propensity score models predict the probability of exposure, DRS predict the
109 probability of the outcome, which in our study was mortality.²⁴ Disease risk scores were
110 calculated using logistic regression. The c-statistic for the final DRS model was 0.91. The full
111 DRS model equation can be found in the footnote of Figure 2. Using nearest neighbor matching
112 within a caliper of 0.25 distance, a single control without replacement was selected for each
113 case.²⁵ We checked DRS balance between cases and controls using graphical displays (Figure
114 2).

115

116 Among patients with at least 90 days of statin therapy in the 90 days prior to admission
117 (proportion of days covered 100% for all patients), the primary exposure of interest was the
118 number of days of continued statin use during admission. The statins included were
119 atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin. A one day gap in
120 therapy was allowed, but the gap was not counted in the calculation of the statin use period. To
121 partition statin continuation days associated with the greatest survival benefit, we conducted a
122 classification and regression tree analysis (CART).^{26,27} The CART analysis, which includes an
123 optimal tree selection based on pruning and cross-validation, identified subsets of patients at
124 lowest risk of death based on days of statin continuation. CART models are useful because of
125 their non-parametric, non-linear structure.²⁷ The trees were automatically developed to forecast
126 inpatient mortality by considering every possible cut-point on statin continuation duration at

127 every node in the classification tree. Based on the split provided by the CART analysis,
128 conditional logistic regression was conducted to calculate the odds of mortality. Statistical
129 analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and R software
130 version 3.2.0 (The R Foundation for Statistical Computing) with a recursive partitioning
131 technique “rpart” package that was developed for Splus (Insightful Corporation, Seattle, WA).²⁸
132 This study was reviewed and approved as exempt by the University of Rhode Island’s
133 Institutional Review Board.
134

135 **Results**

136 Among our study population of prevalent and adherent statin users in the 90 days prior
137 to admission, 61 (6.9%) patients died and 821 (93.1%) survived their hospital stay. Using DRS
138 matching, controls were identified for 58 cases. Due to matching, baseline characteristics were
139 similar between cases and controls, including age (median 68 vs. 67 years, $p=0.8520$; Table 1),
140 gender (39.7% vs. 43.1% females, $p=0.7992$), race (20.7% vs. 15.5% non-whites, $p=0.7637$),
141 and Charlson comorbidity score during the admission (median 4 vs. 4, $p=0.8239$) and in the six
142 months prior to admission (median 4 vs. 4, $p=0.4959$). The length of hospital stay was
143 significantly longer among controls compared to cases (median=9 vs. 5 days, $p=0.0005$). Of the
144 47 (41%) patients who continued statin use during the hospital admission, 32% ($n=15$) were
145 cases and 68% ($n=32$) were controls. The average statin therapy duration during admission
146 among cases and controls was 1.5 ± 3.7 vs. 4.5 ± 7.5 days, respectively.

147

148 The study included an equal number ($n=58$) of cases and controls, producing a 50%
149 survival rate at the root node. The CART analysis partitioned the dependent variable of statin
150 therapy duration at ≥ 2 days. Those continuing statin therapy for at least 2 days had a survival
151 probability of 71.4%, while those not continuing or only continuing for 1 day had a survival
152 probability of 37.8% (Figure 3). The odds of inpatient mortality was 76% lower among those
153 continuing statin therapy for at least 2 days (OR 0.24, 95% CI 0.11-0.55).

154

155

156 **Discussion**

157 In this DRS matched case-control study, we identified a statin continuation duration
158 threshold providing the maximum survival benefit among bacteremic patients. Our findings are
159 consistent with existing literature^{3,4,9} evaluating this association, but we expanded these findings
160 to identify an optimal statin duration of at least 2 days. Though other studies have observed
161 similar protective effects with statin continuation^{3,4,9}, as we observed in our study, duration of
162 pre-admission statin therapy, with and without continuation, not only varied between these
163 studies but also within studies. In considering our findings with those from previous studies, the
164 period of statin exposure is directly related to crucial inflammatory periods, including as the
165 infection develops (pre-admission statin exposure) and the time period right after admission
166 when antibiotics are begun (continued statin exposure for at least those first 2 days).^{29,30}

167
168 A retrospective cohort study among bacteremic patients from a 300-bed acute care
169 hospital in Ipswich, Australia found a reduced adjusted hospital mortality rate (OR 0.39, 95% CI
170 0.17-0.91, p=0.029) in those taking statins prior to admission (n=66), which decreased even
171 further with the continuation of statins (n=56) during the admission (OR 0.06, 95% CI 0.01-0.44,
172 p=0.0056) compared to patients not receiving statins (n=372).³ Pre-admission statin use was
173 based on medication use reported at admission, and therefore duration of prior statin use was
174 not assessed. Similar effect estimates were observed when restricting the analysis to death
175 attributable to bacteremia (statin use only before admission: OR 0.29, 95% CI 0.10-0.86,
176 p=0.025; continued during admission: OR 0.09, 95% CI 0.01-0.64, p=0.016).³ Another
177 retrospective cohort study⁴ conducted among bacteremic patients taking a statin at the time of
178 admission and continuing throughout the hospitalization (n=35) at a Veterans Affairs Medical
179 Center in Washington, identified a therapeutic benefit with statin continuation (adjusted OR
180 0.13, 95% CI 0.02–0.99) compared with patients not taking statins (n=353). Again, duration of
181 pre-admission statin use was not assessed.

182

183 These results should be taken into consideration with clinical judgment with regards to
184 safety as they can contribute to liver dysfunction and life-threatening rhabdomyolysis.^{31,32}
185 Moreover, elevated statin levels have been observed in critical illness, possibly related to
186 pharmacokinetic and pharmacodynamic changes during sepsis but also due to concomitantly
187 prescribed medications with cytochrome P450 inhibition of statin metabolism.^{33,34} Among
188 critically ill patients on continued statins, monitoring of liver function and creatine phosphokinase
189 may be warranted.

190

191 Our study has a number of limitations. First, we were unable to assess statin drug or
192 dose-dependent effects that might affect bacteremic mortality. Second, our study relied on a
193 claims database, which is subject to misclassification due to coding selected for medical claims
194 processing and reimbursement. Third, we could not study differences in mortality by causative
195 pathogen. A previous study²⁴ observed greater protection with statins in *S. aureus* bacteremia
196 compared to bacteremia caused by Gram-negative bacilli, while also suggesting greater survival
197 in nosocomial versus community-associated bacteremia.²⁴ Our study could not evaluate these
198 differences. We also could not distinguish bacteremic severity or changes in oral intake,
199 however, we incorporated potential causative pathogen proxies (identified using ICD-9 codes) in
200 our DRS model, as well as sepsis and ventilation status proxies from diagnosis-related group
201 codes. Moreover, the sample size of our study was small. While we included antibiotic treatment
202 in the DRS mode, we could not evaluate the appropriateness of antibiotic therapy. The intensity
203 of statin therapy was also not assessed. Additionally, the limitations of CART analysis include
204 an inability to fully describe the observed data due to uncertainty that remains in the prediction
205 of the model and potential existence of multiple threshold values despite a single “optimal”
206 split.³⁵ Lastly, since statin use prior to admission was captured from pharmacy dispensings,
207 misclassification due to non-adherence may have impacted our findings.

208

209 In conclusion, we found that continuation of statins for at least 2 days in prevalent,
210 adherent statin users, significantly reduced hospital mortality in our disease risk score matched
211 case-control study conducted in a real-world clinical population. To further understand the
212 relationship between statin use and improved clinical outcomes among those with serious
213 infections, future research should assess drug/dose-response, while accounting for duration-
214 response. Although our findings indicate benefits with continuation of statins during admission,
215 greater information is needed regarding the risks of continuation, in terms of adverse events, to
216 enable a clear benefit-risk assessment.

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Table 1. Demographic and hospitalization-related characteristics in cases and controls

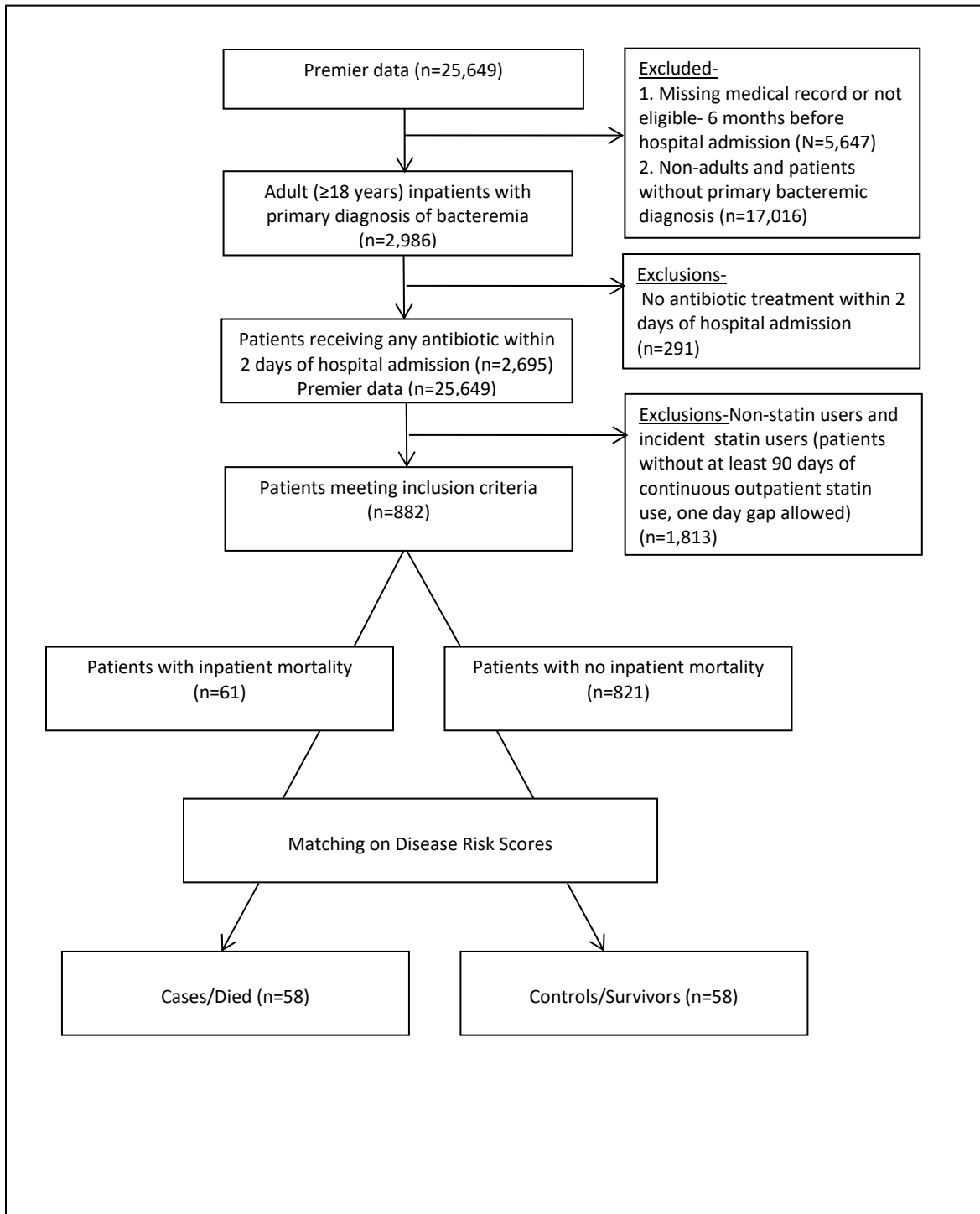
Characteristics	Cases/ Died (n=58)		Controls/ DRS matched survivors (n=58)		P-value
	n/median	%/IQR/sd	n/median	%/IQR/sd	
Age (years)	68	61-77	67	60-82	0.8520
Gender					
Female	23	39.7	25	43.1	0.7061
Male	35	60.3	33	56.9	
Race					
Non-white	12	20.7	9	15.5	0.7637
White	46	79.3	49	84.5	
Admitting physician specialty					
Intensive care/surgery	<5	3.4	<5	3.4	0.9190
Medicine	18	31.0	16	27.6	
Other	38	65.6	40	69.0	
Ventilation status					
Non-ventilation	47	81.0	48	82.8	0.8095
Ventilation	11	19.0	10	17.2	
Hospital admission year					
2010	10	17.3	9	15.5	0.9494
2011	18	31.0	21	36.2	
2012	30	51.7	28	48.3	
Statin therapy during admission					
Average statin therapy duration (days) during admission	1.5	3.7	4.5	7.5	0.0012
Hospital stay					
Length of hospital stay (days)	5	4-6	9	7-11	0.0005
Comorbidities (during admission)					
Charlson score	4	2-6	4	2-7	0.8239
Elixhauser score	6	4-8	6	5-8	
Comorbidities (6 months prior to admission)					
Charlson score	4	2-8	4	1-7	0.4959
Elixhauser score	5	2-8	5	2-8	

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Data are median, standard deviation (sd) and interquartile range (IQR) or number and percent of patients.

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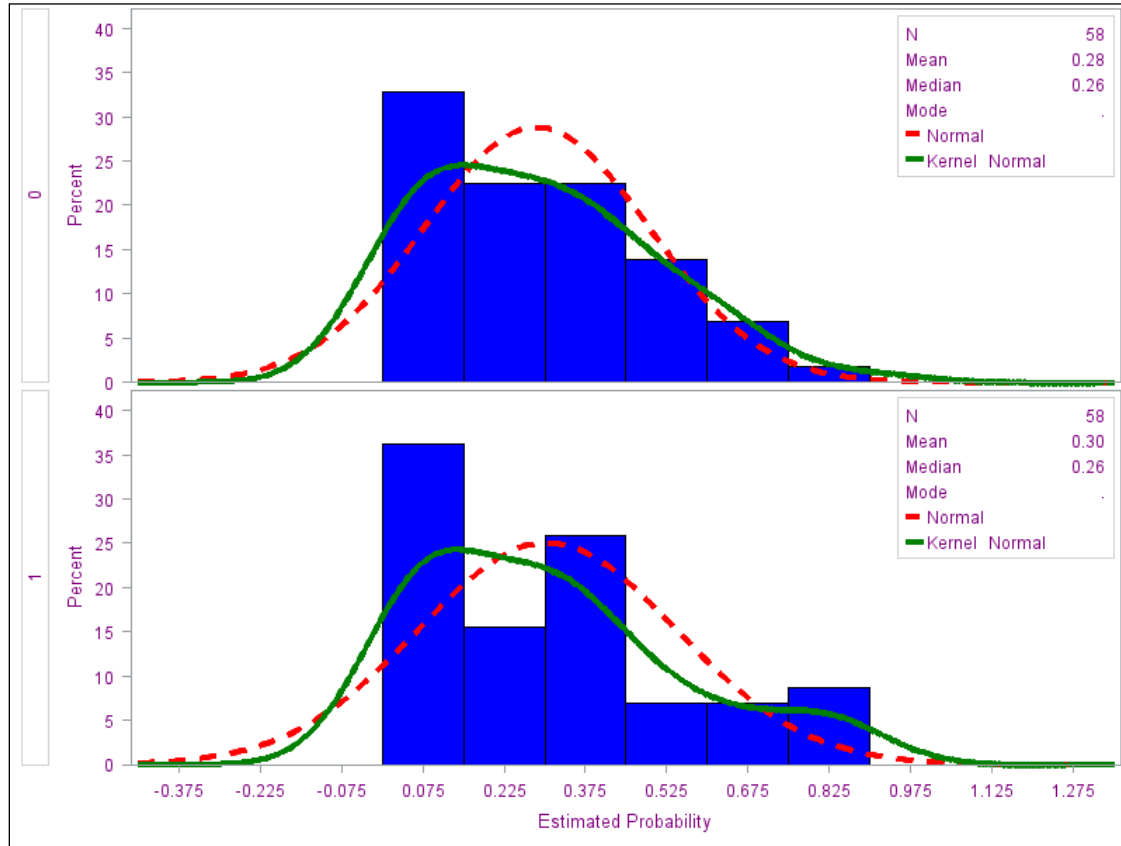
Figure 1: Case-control study design



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Figure 2: Disease risk scores distribution among cases and controls



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Note: On the y-axis, 0 represent controls, while 1 represent cases. On the x-axis, estimated probability is the disease risk score.

238

Variables included in the model: admission type, admission year, admitting physician specialty, age, anemia, antibiotic (initial and other use during admission), census region, Charlson comorbidity score during admission, chronic obstructive pulmonary disease, dyslipidemia, esophageal disorder, fluid and electrolyte disorder, gender, methicillin-resistant *Staphylococcus aureus*, neurological disorder, nutritional endocrine metabolic disorder, payor, race, sepsis, shock, ventilation, history of peripheral vascular disease, history of anemia, history of gastrointestinal disorders.

245

Disease risk score (DRS):

247
248 The disease risk score was the calculated probability of inpatient mortality among the unexposed group.
249 Associations between the dependent variable (inpatient mortality) and independent variables
250 (demographic, clinical, and hospitalization-related characteristics) were assessed with logistic
251 regression. Variables with likelihood ratio test p-values <0.25 were included in the initial multivariate
252 logistic regression model and then removed using step-wise backward elimination to arrive at the final
253 DRS model, with all remaining p-values <0.05. The final DRS model was then used to calculate DRSs for
254 the exposed group. Absence of multicollinearity was confirmed, as was goodness of fit. Using nearest
255 neighbor matching within a restricted caliper distance of 0.25, one control was selected per case.

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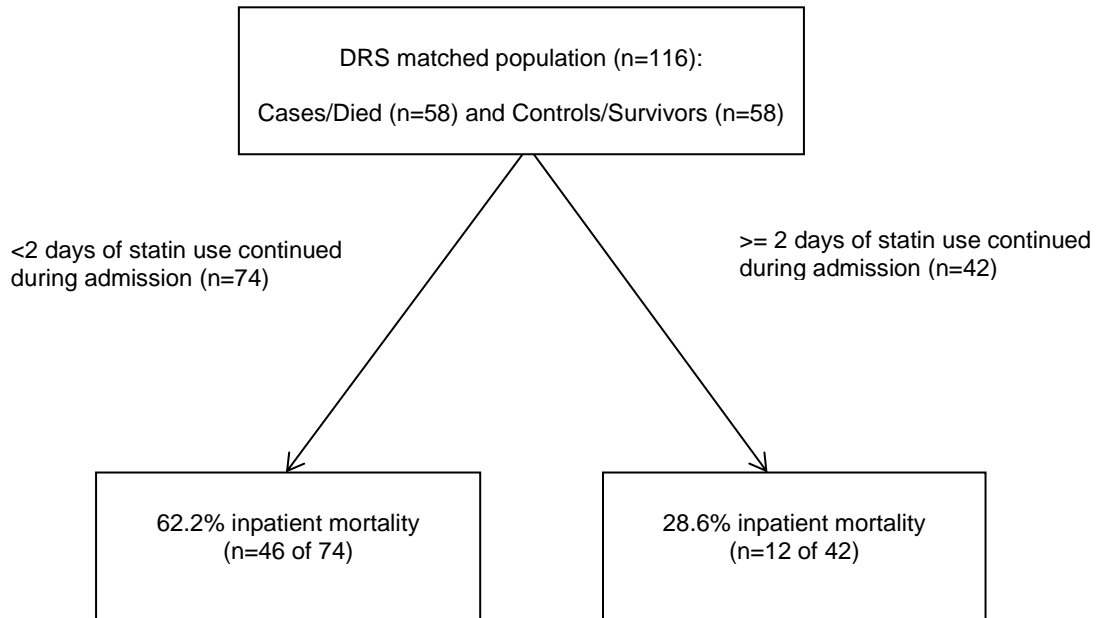
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272 **Figure 3: Partitioning from CART analysis**
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