

1 **Predicting 30-day mortality in patients with Sepsis; an exploratory**  
2 **analysis of process of care and patient characteristics**

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22 **Keywords**

23 Sepsis, mortality, survival, prediction, epidemiology

24 **Ethics, consent and permissions**

25 Observational quality improvement project prospectively reviewed by the Nottingham  
26 University Hospitals NHS Trust Research and Innovation Committee in 2004. Permission  
27 granted for data collection and reporting of results by the Caldicott Guardian. The need  
28 for ethical review was waived. The project was registered with the audit office,  
29 registration number 2890. All patient identifiable metrics removed from data prior to  
30 analysis.

31 **Declarations of interest**

32 MJRS was an unpaid member of the NICE Sepsis (CG51) Guideline Development Group.  
33 All other authors, no conflicts to declare.

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35 **Abstract – Word Count 243**

36 **Background:** Sepsis represents a significant public health burden, costing the NHS  
37 £2.5 billion annually, with 35% mortality in 2006. The aim of this exploratory study was  
38 to investigate risk factors predictive of 30-day mortality amongst patients with sepsis in  
39 Nottingham.

40 **Methods:** Data was collected prospectively from adult patients with sepsis in  
41 Nottingham University Hospitals NHS Trust as part of an on-going quality improvement  
42 project between November 2011 and March 2014. Patients admitted to critical care with  
43 the diagnosis of sepsis were included in the study. 97 separate variables were  
44 investigated for their association with 30-day mortality. Variables included patient  
45 demographics, symptoms of SIRS (systemic inflammatory response syndrome), organ  
46 dysfunction or tissue hypoperfusion, locations of early care, source of sepsis and time to  
47 interventions.

48 **Results:** 455 patients were included in the study. Increased age (adjOR=1.05  
49 95%CI=1.03-1.07  $p<0.001$ ), thrombocytopenia (adjOR=3.10 95%CI=1.23-7.82  
50  $p=0.016$ ), hospital-acquired sepsis (adjOR=3.34 95%CI=1.78-6.27  $p<0.001$ ), increased  
51 lactate concentration (adjOR=1.16 95%CI=1.06-1.27  $p=0.001$ ), remaining hypotensive  
52 after vasopressors (adjOR=3.89 95%CI=1.26-11.95  $p=0.02$ ) and mottling (adjOR=3.80  
53 95%CI=1.06-13.55  $p=0.04$ ) increased 30-day mortality odds. Conversely, fever  
54 (adjOR=0.46 95%CI=0.28-0.75  $p=0.002$ ), fluid refractory hypotension (adjOR=0.29  
55 95%CI=0.10-0.87  $p=0.027$ ) and being diagnosed on surgical wards (adjOR=0.35  
56 95%CI=0.15-0.81  $p=0.015$ ) were protective. Treatment timeliness were not significant  
57 factors.

58 **Conclusion:** Several important predictors of 30 day mortality were found by this  
59 research. Retrospective analysis of our sepsis data has revealed mortality predictors  
60 which appear to be more patient related than intervention specific. With this information,  
61 care can be improved for those identified most at risk of death.

62 **Introduction**

63 Sepsis is defined as life threatening organ dysfunction resulting from a dysregulated host  
64 response to infection [1] and represents a significant burden to UK healthcare. Between  
65 5.1% and 7% of all deaths in the UK are associated with sepsis [2], costing the NHS  
66 £2.5 billion annually [3]. Sepsis is the second highest cause of mortality in the UK, with  
67 between 36,000 to 64,000 people dying per year [4].

68 Following “unacceptably high” [5] mortality rates from sepsis (and associated historical  
69 terms severe sepsis), the *Surviving Sepsis Campaign* set out to standardise treatment  
70 through protocols. Early Goal Directed Therapy (EGDT) detailed interventions for treating  
71 patients with sepsis and their time-frame. After multiple permutations of the guidelines,  
72 and their latest revision in 2016, the current recommendations include time critical  
73 administration of antimicrobial therapy and cardiovascular resuscitation (target within 1  
74 hour and 3 hours respectively) [1]. Initial studies showed improved in hospital mortality  
75 for septic patients treated with EGDT [6]. However, subsequent research including three  
76 large clinical trials and their associated meta-analysis, have shown no significant  
77 improvement in patient outcome when using EGDT [7–10], undermining initial treatment  
78 strategies.

79 Despite the overwhelming burden of the disease, slow progress on treatment strategies  
80 has prompted calls for further research into sepsis. In particular, more knowledge is  
81 required of the factors that increase the risk of death from sepsis, in order to guide  
82 treatment protocols and delivery of care, and ultimately reduce sepsis-associated  
83 mortality. This exploratory study aims to investigate patient factors, signs, symptoms  
84 and process of care and their association with 30 day mortality.

85

86 **Methods**

87 Data was prospectively recorded between November 2011 and March 2014 on adult  
88 patients with sepsis presenting Nottingham University Hospitals NHS Trust, as part of an  
89 ongoing quality improvement project in managing sepsis since 2005. Patients were  
90 identified as those admitted to the critical care department including the intensive care  
91 unit, and both the medical and surgical high dependency units with the diagnosis of  
92 sepsis [11]. Inclusion criteria were based on the penultimate consensus definition for  
93 severe sepsis, with presence of two or more signs of the systemic inflammatory response  
94 syndrome (SIRS) and one or more sign of organ dysfunction or tissue hypoperfusion  
95 with a background of proven or suspicion of infection. Confirmatory blood culture was  
96 not an inclusion criterion. Patients were excluded if they were transferred from another  
97 hospital with pre-existing sepsis.

98 A dedicated sepsis team collected the information using a previously validated data  
99 collection tool [12]. Variables included patient demographics, symptoms of SIRS,  
100 markers of organ dysfunction or tissue hypoperfusion, source of sepsis, locations of early  
101 care, and time to interventions. These 97 variables were then assessed for association  
102 with 30 day mortality, the primary outcome (online supplement Table E1). Data on 30  
103 day mortality was collected routinely from the hospital administrative system, including  
104 both hospital and community deaths. Time zero was the time of the initial symptom, sign  
105 or indicator of organ dysfunction or tissue hypoperfusion due to severe sepsis.

106 Basic characteristics were obtained using summary statistics and univariate analyses.  
107 Chi<sup>2</sup> and Fisher's exact test were used to assess categorical variables. Independent  
108 samples t-test and Mann-Whitney test were used for continuous data, as appropriate.

109 A multi-variate model was built including all those variables that were significant  
110 predictors of 30 day mortality ( $p < 0.05$ ). Those variables that that were no-longer  
111 significant were removed, then each non-significant variable was added individually to  
112 the model and keeping significant variables. Likelihood-ratio test determined the

113 significance of categorical variables in terms of 30 day mortality. For all tests, a  
114 significance level of  $p < 0.05$  was used. All data was analysed in Stata (version 13)  
115 The data collection was registered under the Nottingham University Hospitals Audit  
116 Office, with the reference number 2890. Initial permission for data collection was  
117 granted in 2004, with an institutional waiver for informed consent. For analysis, data  
118 was anonymised, with all patient-identifiers removed from the database.

## 119 **Results**

120 455 patients were identified with severe sepsis, with 26.2% mortality. Age ranged from  
121 17 to 95 and mean age was 64.0 years (standard deviation=16.6). 42% of patients were  
122 female.

123 Following univariate analysis for association with 30 day mortality (Online table E1-E11),  
124 fever ( $>38.3^{\circ}\text{C}$ ) (OR=0.35 95%CI=0.23-0.55), (Table E2, additional file), sepsis from  
125 skin infection (OR=0.34 95%CI=0.12-0.99), (Table E5, additional file), and not needing  
126 inotropes within 6 hours (OR=0.36 95%CI=0.15-0.89), (Table E10, additional file), were  
127 shown to be protective. Increased age (Table E1, additional file), hypothermia (core  
128 temperature  $<36^{\circ}\text{C}$ ) (OR=3.44 95%CI=1.83-6.45), (Table E2, additional file), altered  
129 mental status (OR=1.88 95%CI=1.14-3.10), (Table E2, additional file), coagulation  
130 abnormalities (OR=2.94 95%CI=1.00-8.61), (Table E3, additional file),  
131 thrombocytopenia (platelet count  $<100 \times 10^9/\text{L}$ ) (OR=2.85 95%CI=1.32-6.15), (Table  
132 E3), mottling of the skin (OR=4.50 95%CI=1.55-13.08), (Table E3, additional file),  
133 elevated serum lactate concentration (Table E8, additional file), remaining hypotensive  
134 after vasopressors (OR=3.80 95%CI=1.53-9.40), (systolic blood pressure  $<90\text{mmHg}$  or  
135 mean arterial pressure  $<70\text{mmHg}$ ) (Table E9, additional file) and hospital acquired  
136 sepsis (symptoms first shown  $>24$ hours after hospital admission with different  
137 diagnosis) (OR=1.80 95%CI=1.11-2.94), (Table E11, additional file) were shown to  
138 increase odds of 30 day mortality.

139 Multivariate analyses (Table 1) demonstrated increasing age (OR per year increase=1.05  
 140 95%CI=1.03-1.07), thrombocytopenia (OR=3.10 95%CI=1.23-7.82), higher lactate  
 141 value (OR per mmol increase=1.16 95%CI=1.06-1.27), remaining hypotensive after  
 142 vasopressor treatment (OR=3.89 95%CI=1.26-11.95), hospital-acquired sepsis  
 143 (OR=3.34 95%CI=1.78-6.27) and mottling (OR=3.80 95%CI=1.06-13.55) to be  
 144 predictors of increased odds of 30 day mortality. In addition, fever (OR=0.46  
 145 95%CI=0.28-0.75), being on a surgical ward at the time of sepsis presentation  
 146 (OR=0.35 95%CI=0.15-0.81 and fluid refractory hypotension as defined by the 2008  
 147 and subsequently 2012 Surviving Sepsis Campaign guidelines, (OR=0.29 95%CI=0.10-  
 148 0.87) were shown to be protective against 30 day mortality. No process of care factors  
 149 was significant in either univariate or multivariate analysis.

150 **Table 1: Multivariate logistic regression model indicating variables significantly**  
 151 **associated with 30 day mortality**

<b>Variable</b>	<b>OR<sup>a</sup></b>	<b>AdjOR*</b>	<b>95%CI<sup>b</sup></b>	<b>p-value</b>
<b>Age (per year)</b>		1.05	1.03-1.07	<0.001
<b>Temperature &gt;38.3°C</b>	0.35	0.46	0.28-0.75	0.002
<b>Thrombocytopenia (&lt;100x10<sup>9</sup>/L)</b>	2.85	3.10	1.23-7.82	0.016
<b>Hospital-acquired sepsis</b>	1.80	3.34	1.78-6.27	<0.001
<b>Lactate Value (per mmol/L)</b>		1.16	1.06-1.27	0.001
<b>Fluid Refractory Hypotension<sup>c</sup></b>	0.60	0.29	0.10-0.87	0.027
<b>Remain in Hypotensive State<sup>cd</sup></b>	3.80	3.89	1.26-11.95	0.02
<b>Surgical Ward at Time Zero</b>	0.57	0.35	0.15-0.81	0.015
<b>Mottling of the skin</b>	4.50	3.80	1.06-13.55	0.04

152 <sup>a</sup> Odds Ratio

153 \*Adjusted Odds Ratio- mutually adjusted for everything in the table

154 <sup>b</sup>95% Confidence Interval

155 <sup>c</sup> Persistent systolic blood pressure <90mmHg or mean arterial pressure <70mmHg despite fluid  
 156 resuscitation

157 <sup>d</sup>15 patients missing data

158

## 159 **Discussion**

160 Although there were a number of factors investigated, only 9 variables were predictors  
161 of 30 day mortality, and none of these were process of care variables such as timeliness  
162 of care, or seniority of doctor. Important predictors were increased age,  
163 thrombocytopenia ( $<100 \times 10^9$ ), hospital-acquired sepsis, increased serum lactate  
164 concentration, remaining hypotensive following vasopressors and mottling of the skin, all  
165 of which increased odds of 30 day mortality. In our data set, temperature  $>38.3^\circ\text{C}$ , fluid  
166 refractory hypotension and being on a surgical ward were protective against 30 day  
167 mortality. With the exception of fluid refractory hypotension proving significantly  
168 protective, these variables are largely consistent with other research(13–15).

### 169 **Age**

170 There are two reasons why older age may be associated with increased mortality in  
171 patients with sepsis. First, with increased age is associated with decreased lymphocyte  
172 function, causing weakened immune responses [16]. This is compounded by poor  
173 nutritional status and altered cytokine response [17]. The second possibility is that older  
174 patients have more comorbidities (itself an independent risk factor for death from sepsis  
175 [18]).

### 176 **Temperature $>38.3^\circ\text{C}$**

177 Fever may be associated with improved outcomes for both pathophysiological and care-  
178 process reasons. Fever has been associated with better outcomes in other studies  
179 including the *FACE Study Group* [13], which found the odds ratio for mortality associated  
180 with fever ( $37.5^\circ\text{C}$ - $38.4^\circ\text{C}$ ) was 0.45 ( $p=0.014$ ), almost identical to the odds ratio found  
181 in this research. Fever enhances immune cell activity, with increased cytokine production  
182 [19], and inhibits pathogen growth, improving survival [13,20,21]. Additionally, as a  
183 widely recognised symptom and sign of sepsis even amongst non-healthcare  
184 professionals, fever may result in earlier recognition and faster treatment, which may in  
185 turn be beneficial for survival.



186

187 **Thrombocytopenia (<100x10<sup>9</sup>/L)**

188 The finding that thrombocytopenia was significantly associated with 30 day mortality in  
189 septic patients, with an odds ratio of 3.1, is supported by other research [22–24]. *Lee et*  
190 *al* found that platelet count was significantly higher in survivors of sepsis than those who  
191 died (194+/-27x10<sup>9</sup>/L versus 97+/-18x10<sup>9</sup>/L, *p*<0.004), concluding also that  
192 thrombocytopenia is an independent risk factor for mortality in septic patients. Indeed  
193 low platelet count is included as a marker of poor prognosis in the SOFA score  
194 (sequential organ failure assessment), used to assess severity of organ failure [25].

195 **Lactate value**

196 Elevated lactate is either a marker of reduced global perfusion and tissue hypoxia with  
197 associated anaerobic cellular respiration or reduced hepatic clearance of lactate [26].  
198 Previous studies have shown a linear relation between increased lactate and increased  
199 mortality [14], in accordance with our finding that increased serum lactate is a marker  
200 poor prognosis.

201 **Mottling of the skin**

202 Mottling (*livedo reticularis*) is caused by peripheral blood vessel constriction [15].  
203 Previous studies have demonstrated an association between skin mottling and mortality  
204 [15,27]. One theory suggests that mottling reflects microvascular abnormalities,  
205 associated with organ dysfunction from microvascular shunting and hypoperfusion, and  
206 therefore increased mortality from multiple organ failure.

207 **Fluid refractory hypotension (septic shock)**

208 In this study, the mortality rate of patients with septic shock at 30 days was 23.9%,  
209 which is at the lower end of previous mortality estimates (22%-50%(28,29)). However,  
210 these studies above do not distinguish between patients who did not respond to  
211 vasopressor therapy, found to increase odds of 30 day mortality (see below), and

212 patients who did respond. Therefore, the difference in observed mortality rates may be  
213 explained by the proportion of patients who remained hypotensive after receiving fluid  
214 and subsequent vasopressors. Another plausible argument of the apparently protective  
215 characteristic of septic shock is that it may represent the beneficial effect of expedient  
216 transfer of patients into critical care to receive vasopressor therapy, which is otherwise  
217 unavailable within the hospital. In this data set, 247 patients remained hypotensive after  
218 fluid therapy, with a median average time of admission to critical care of 6 hours (inter  
219 quartile range [IQR] 3.86-10 hours) compared to 97 patients who responded to fluid with  
220 a median average admission time of 7 hours (IQR 4.25-14.3 hours). The wide range of  
221 times and presence of outliers; fluid refractory 0-80 hours, and fluid responsive 0-244  
222 helps to explain why this demonstrated a trend towards statistical significance with  
223  $p=0.0527$ .

#### 224 **Remaining hypotensive after vasopressor treatment**

225 Fluid and vasopressor refractory hypotension was associated with increased mortality. In  
226 combination with the previous finding that fluid refractory hypotension was protective,  
227 this may indicate that prognosis is only poor in patients with septic shock, who fail to  
228 respond to vasopressors.

#### 229 **Hospital-acquired sepsis**

230 The care of septic patients admitted to critical care from wards rather than emergency  
231 departments seems to be less well established, leading to higher in-hospital mortality  
232 [30]. This supports our findings of an increased 30 day mortality in patients diagnosed  
233 with severe sepsis on wards rather than from emergency admission areas such as the  
234 Emergency Department or acute admission unit. Additionally, comorbidity and reason for  
235 hospital stay may itself cause higher mortality within this population.

#### 236 **Patient on surgical ward at time of diagnosis of sepsis**

237 Diagnosis of sepsis in patients on a surgical ward was found to be associated with a reduction  
238 in 30 day mortality. Surgical patients may have a source of sepsis more amenable to

239 source control through surgical management, such as debridement or drainage,  
240 improving survival prospects compared to medical patients in whom source control is  
241 impossible to achieve, for example in severe pneumonia. Additionally, as sepsis is a  
242 known complication of surgery [31,32], it is also possible that clinicians are more  
243 receptive of the signs and symptoms necessary to facilitate rapid diagnosis.

#### 244 **Process of Care Factors**

245 Process of care factors, such as time delay to be seen, seniority of assessing clinician,  
246 and time delay to intervention were not found to significantly affect 30 day mortality.  
247 This contradicts much of the early research into sepsis care [6,33,34], which formed the  
248 foundations of EGDT and subsequent sepsis care bundles. However, recent research  
249 including a systematic review [10] of three large clinical trials [7–9] also found no  
250 significance between mortality and EGDT. It also must be considered that the apparent  
251 lack of significance between the process of care factors and 30-day mortality may be due  
252 to the low variability of care provided at our institution following over a decade of service  
253 improvement in the care of patients with sepsis. This has included hospital wide  
254 screening systems, multi-specialty and multi-disciplinary education programs, audit and  
255 performance related feedback by a dedicated sepsis team. Therefore, whilst these  
256 process factors such as time to treatment may still be significant with large variation in  
257 practice, this was not detectable in this study. This is reinforced by the recent findings of  
258 Seymour and colleagues [35].

#### 259 **Strengths and limitations**

260 Exclusion criteria were minimised, making the study population representative of  
261 patients in Nottingham. As the fourth largest acute trust in the UK, the results of this  
262 study are highly generalizable to the rest of the UK. Missing data was low and the study  
263 took place in a real-world setting. Data collection was carried out by a trained and  
264 dedicated sepsis team with over a decade of experience in using the data collection

265 tools. It is important to note that this sepsis team were not involved in treatment of  
266 these patients.

267 Limitations of this study include the large number of tests carried out, increasing chance  
268 of false positive findings. If Bonferroni correction was applied only those results with a  $p$ -  
269 value of  $<0.0005$  would be considered significant. This work was carried out as an  
270 exploratory study and therefore further work with larger data sets would be required to  
271 confirm the findings of interest. For the duration of this work, the historical penultimate  
272 sepsis definitions were used [11]. Although the term severe sepsis is no longer used and  
273 the definition of septic shock has changed, it is felt that the results of this study are still  
274 applicable as the core disease processes underpinning the definition have not changed.

275 It is important to realise a significant limitation of this study is the apparent selection  
276 bias involved in patient identification of only those admitted to critical care areas with  
277 the diagnosis of sepsis. This risks omitting a group of patients who were treated  
278 appropriately with good response demonstrating early resolution of organ dysfunction.  
279 However, this method of identification yields similar numbers compared to previous work  
280 at Nottingham University Hospitals NHS Trust [12], this may be explained by evolving  
281 practice in terms of managing patient acuity, disease severity and patient flow through  
282 the hospital pathways such that a greater proportion of unwell patients are managed on  
283 critical care than a decade ago.

## 284 **Conclusion**

285 In conclusion, this exploratory analysis presents the factors significantly associated with  
286 30 day mortality in patients diagnosed with sepsis. Results suggest importance of patient  
287 factors associated with mortality. Age, thrombocytopenia, remaining hypotensive after  
288 vasopressor administration, hospital-acquired sepsis, increased serum-lactate  
289 concentration and mottling all increased odds of 30 day mortality. Presentation on a  
290 surgical ward, fever and septic shock were found to be protective. This paper highlights  
291 some interesting risk factors associated with mortality from sepsis, indicating the

292 direction of further research, particularly into the seldom researched matter of hospital  
293 acquired sepsis.

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