

1 **Clinical Presentation, Biochemical and Haematological Parameters and their Association with Outcome in**
2 **Patients with Ebola Virus Disease: An observational Cohort Study**

3

4 **Short title:**

5 Laboratory abnormalities in EVD

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31

32 **Abstract**

33 **Background**

34 Clinical management of Ebola Virus Disease (EVD) remains challenging. Routine laboratory analytics are
35 often unavailable in the outbreak setting, and few data exist on the associated haematological and
36 biochemical abnormalities. We present laboratory and clinical data from the Kerry Town Ebola Treatment
37 Centre in Sierra Leone to better inform clinical management algorithms, improve understanding of key
38 variables associated with outcome and provide insight into the pathophysiology of EVD.

39 **Methods**

40 150 patients with confirmed EVD were admitted between 8th December 2014 and 9th January 2015. At
41 admission, all patients had clinical presentation recorded and blood taken for Ebola confirmation using
42 reverse-transcriptase–polymerase-chain-reaction (RT-PCR) and for haematological and biochemical
43 analysis. The association between these and clinical outcome was evaluated.

44 **Findings**

45 The mean age of cases was 26 years. Case fatality rate was 35% (55/150). Most patients presented with
46 stage 2 (gastrointestinal involvement, 61%, 72/118) and stage 3 (severe/complicated, 10%, 12/118)
47 disease. Acute Kidney injury (AKI) was common (50%, 52/104), as were abnormal serum potassium (33%,
48 32/97), severe hepatitis (59%, 54/92) and raised CRP (21%, 21/100). Haematological abnormalities were
49 common, including raised haematocrit (15%, 15/100), thrombocytopenia (45%, 47/104) and
50 granulocytosis (42%, 44/104). Severe AKI, low RT-PCR cycle threshold (<20 cycles) and severe hepatitis
51 were independently associated with mortality.

52 **Interpretation**

53 EVD is associated with a high prevalence of haematological and biochemical abnormalities, even in mild
54 disease and in the absence of gastrointestinal symptoms. Clinical care targeting hypovolaemia, electrolyte
55 disturbance and AKI are likely to reduce historically high case fatality rates.

56 **Funding**

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58

59

60 **Introduction**

61 Ebola virus disease (EVD) is caused by an RNA Filovirus, and is characterised by a febrile illness (87%), often
62 progressing to diarrhoea (67%), vomiting (66%) and, sometimes, haemorrhage (18%).¹ The current
63 outbreak in West Africa is the largest the world has seen, with almost 25,000 cases (25th March 2015).²
64 Clinical and public health management is challenging, especially in the worst hit countries of Sierra Leone,
65 Liberia and Guinea, due to severity of clinical presentation, infection control concerns, poor health-system
66 infrastructure and high population density.^{3,4}

67
68 There are currently no proven treatments for EVD, thus management is supportive, including
69 administration of oral and intravenous fluids and electrolytes, management of co-infections and symptom
70 control.³⁻⁵ EVD is recognised to cause marked biochemical abnormalities which may be amenable to simple
71 interventions, potentially reducing the high case fatality rate (CFR).^{4,6-12} Due to the low-resource setting of
72 outbreaks and risks associated with collecting and processing laboratory samples, few data exist on these
73 abnormalities, mostly from animal models, small cohorts or case studies from resource-rich settings.^{6-9,11,13}

74
75 Kerry Town Ebola Treatment Centre (ETC), operated by Save the Children, opened on November 5th 2014 in
76 Sierra Leone offering supportive care focused on fluid and electrolyte management, in accordance with
77 World Health Organization (WHO) guidelines.³ This included haematology and biochemistry testing for all
78 admissions from December 8th 2014. We report data on clinical presentation, laboratory abnormalities, and
79 their association with mortality in patients admitted over a one month period. This data will assist in case
80 management in centres without access to laboratory support, provide insight into the disease
81 pathophysiology, corroborate animal models, and help identify priority areas for future research.

82
83 **Methods**

84 **Study Design**

85 We conducted a cohort study of patients consecutively admitted to Kerry Town ETC between 8th December
86 2014 and 9th January 2015. During this period only patients with EVD confirmed at other isolation or
87 community care centers were admitted. We used a standard case definition as per WHO guidelines.² All
88 patients were included in the study except for those who were dead on arrival, or those who had no blood
89 results within 24 hours of admission. Primary outcome measure was discharge from the ETC.

90
91 **Blood Analysis**

92 Samples were analysed at the on-site laboratory run by Public Health England and the UK Defence Medical
93 Services (UK-DMS). The Piccolo Express® system (Abaxis, California, USA) was used to generate metabolic
94 and liver function profiles. An assay with biochemistry and liver function profile was primarily used

95 (Amylyte 13), though some samples were processed on a separate assay that included lactate, magnesium,
96 calcium and phosphate but excluded liver function profile (Metlac 12). Laboratory scientists selected the
97 assay based on availability, unless clinically requested. Haematology samples were processed using a
98 Horiba ABX Micros ES60[®] analyser (Horiba, Montpellier, France). Reverse-transcriptase-polymerase-chain-
99 reaction (RT-PCR) assays for diagnosis of EBOV were performed using the Altona RealStar[®] Filovirus RT-PCR
100 Kit (Altona, Hamburg, Germany), following inactivation and manual RNA extraction. Positive results were
101 reported as Ct (cycle threshold) values. All patients had a repeat RT-PCR on admission.

102

103 **Data Collection**

104 All data was collected as part of routine patient care, and recorded on standardised forms, which were kept
105 securely. Data extracted for research purposes was anonymised and stored on a password-protected
106 database. The Sierra Leone Ethics and Scientific Review Committee provided study approval.

107

108 **Clinical Staging and management**

109 All patients were assigned a disease stage on admission according to their clinical features. The staging
110 system was developed by the UK-DMS in reference to WHO guidelines and the proposed pathogenesis of
111 EVD and is outlined in Table 1.^{3,12-15} Children were staged using a similar system, informally adapted to
112 include paediatric indicators of dehydration as per WHO.³ Standardised therapy was administered to all
113 patients based on disease stage. Targeted electrolyte replacement was provided based on biochemistry
114 results. Patients were discharged once asymptomatic for 72 hours with negative repeat blood Ebola RT-
115 PCR. Acute Kidney Injury (AKI) was defined according to RIFLE criteria.¹⁶ To estimate baseline creatinine, we
116 used the Modification of Diet in Renal Disease (MDRD) for adults,¹⁷ and the Schwartz calculation for
117 children.¹⁸ For ALT and AST, 'high' was defined as 5-15 times the upper limit of normal (ULN), and 'very
118 high/severe' was defined as >15 times ULN. EBOV RT-PCR Ct value (Ct) was categorised as low (<20 cycles)
119 or high (≥20 cycles) with low Ct indicating high viral load.

120

121 **Statistical Analysis**

122 Descriptive analyses are reported as frequencies, proportions, means or medians. We used χ^2 , t-test and
123 Wilcoxon rank-sum for comparisons. Risk factors for mortality were assessed using logistic regression. A
124 *priori* variables, and variables associated with mortality in univariate analysis (at $p < 0.1$) were assessed in a
125 multivariate model. Interactions were assessed using likelihood ratio tests. Adjustment was not made for
126 missing data since biochemical and haematological variables were missing at random. Hypothesis tests
127 were two-tailed (at $p < 0.05$). Data was analysed using Stata (Statacorp, Texas, USA), v13.

128

129 **Role of the Funding Source**

130 The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or
131 writing of the report. The corresponding author had full access to the data in the study and had final
132 responsibility for the decision to submit for publication.

133

134 **Results**

135 During the study period, 150 patients were admitted with confirmed EVD. Additionally 6 non-EVD cases
136 were referred and 4 patients died in transit. Absent laboratory samples were due to no sample being
137 obtained on admission (n=8) and a laboratory isolator fault meaning no samples were processed from 26th-
138 29th December (n=24). Of the 118 included patients, 104 had haematology and 114 had biochemistry
139 analysed. In these patients, absent tests were due to no haematology sample being taken (n=12),
140 haematology sample inadequate for analysis (n=2) or no biochemistry sample taken (n=4). 101 patients had
141 liver function analysed and 18 had lactate measured, with 5 having both.

142

143 Baseline characteristics are described in Table 2. Among EVD cases, 52.5% were male. The mean age was
144 25.9 years (sd 14.7). Children (<18 years) accounted for 32.2%. Median time from admission to discharge
145 amongst survivors was 8 days (inter quartile range (IQR) 5-12) and median time from admission to death
146 was 4 days (IQR 3-5). Patients without laboratory investigations were more likely to be under 5 years
147 (p=0.003) and female (p=0.033) but otherwise had similar baseline characteristics to those with laboratory
148 results.

149

150 **Mortality**

151 Overall CFR for the study period was 36.7% (55/150). CFR in those included in this study was 34.7%
152 (41/118). CFR was non-significantly higher in men than women (40.3% vs. 28.6%. $X^2=1.79$, p=0.181) and
153 lower in children (23.7% vs. 40.0%, $X^2=3.02$, p=0.082). Higher disease stage on admission was strongly
154 associated with mortality (66.7%, 32.7% and 25.8% for stage 3, 2 and 1 respectively, p=0.001). Mean time
155 from symptom onset to admission was shorter in patients who died than in survivors. There was no
156 association between time from symptom onset and disease stage at admission.

157

158 **RT-PCR Ct values**

159 The mean Ct in positive patients was 21.4 cycles (sd 4.5), with 41.1% (46/112) having a low Ct. Low Ct on
160 admission was strongly associated with mortality (65.2% vs. 13.6%, p<0.001). Fifteen patients were
161 transferred following positive EBOV RT-PCR tests at the referring center, but tested negative at admission,
162 despite remaining symptomatic. Their survival rate was 100%.

163

164 **Biochemistry**

165 Biochemistry results for the cohort are outlined in Table 3 and Figure 1. Creatinine levels were significantly
166 higher in fatal than non-fatal cases (median 467 μ mol/L vs. 90 μ mol/L respectively, $p<0.001$, $n=104$). AKI was
167 common, occurring in 50.0% (52/104) of cases. AKI occurred more commonly in fatal than non-fatal cases
168 (81.3% vs. 18.1%, $p<0.001$) and when it did occur it was always severe (RIFLE-3). Incidence of AKI did not
169 differ significantly by clinical stage ($\chi^2= 9.83$, $p=0.610$). Notably, 28.6% (9/31) of patients admitted with
170 stage 1 disease had severe AKI.

171

172 Abnormal potassium occurred in 33.0% (32/97) of admissions, with similar proportions having
173 hypokalaemia and hyperkalaemia (19.6%, 19/97 and 13.4%, 13/97 respectively). Patients that died were
174 more likely to have hyperkalaemia (35.7% vs. 4.4% of survivors, $p<0.001$), as were patients with AKI (26.7%
175 with RIFLE-3 AKI vs. 6.5% with no AKI or RIFLE 1-2 AKI, $p=0.007$). Hyponatraemia was common (31.9%,
176 36/113), but was not associated with outcome. Abnormal liver function was common, with 70.3% (71/101)
177 having alanine transaminase (ALT) or aspartate transaminase (AST) >5 times ULN. Severe hepatitis (AST >15
178 ULN) was more common in fatal than non-fatal cases (92.9% vs. 43.8% respectively, $p<0.001$). Median
179 AST:ALT ratio was 2.3, and did not differ significantly between outcomes. Bilirubin was normal in 87.0% of
180 cases.

181

182 Raised creatinine kinase (CK) was common, and higher in fatal than non-fatal cases (median CK 2938 IU/L
183 versus (vs.) 1519 IU/L, $p=0.019$, $n=100$). All cases with a normal CK survived. Fourteen cases had CK >5000
184 IU/L (upper limit of our assay). Almost all cases with RIFLE-3 AKI had raised CK (97.1% vs. 78.3% with no AKI,
185 $p=0.014$). Median C-reactive protein (CRP) was higher in fatal than non-fatal cases (median CRP 12.9 vs.
186 69.5, $p<0.001$, $n=100$), and more fatal cases had CRP >100 mg/L (46.9% vs. 8.8% in survivors, $p<0.001$).
187 Lactate was raised in 91.7% (16/17) of cases.

188

189 Haematology

190 Haematology results for the cohort are outlined in Table 3 and Figure 1. Higher mean haemoglobin (Hb),
191 haematocrit (Hct) and median platelet count were associated with mortality. Mean Hb, Hct and platelets in
192 non-survivors versus survivors were 15.5g/dl vs. 13.5g/dl ($p<0.001$, $n=103$) 45.1 vs. 39.4% ($p<0.001$, $n=100$)
193 and 146×10^9 /L vs. 197×10^9 /L ($p=0.005$, $n=104$) respectively. Thrombocytopenia was more common
194 amongst non-fatal cases (53.7% vs. 29.7%, $p=0.019$). Severe thrombocytopenia ($<50 \times 10^9$ /L) was
195 uncommon (2.9%, 3/104).

196

197 Low median white cell count (WCC), lymphocyte count and granulocyte count also predicted survival.
198 Median WCC was 15.8×10^9 /L vs. 7.9×10^9 /L, ($p<0.001$, $n=104$) median lymphocytes were 4.2×10^9 /L vs. $2.2 \times$
199 10^9 /L ($p<0.001$, $n=104$) and granulocytes were 11.5×10^9 /L vs. 4.3×10^9 /L ($p=0.001$, $n=104$) in non-survivors

200 vs. survivors respectively. Granulocytosis was present in 42.3% (44/104) of cases, and lymphocytosis was
201 more common in fatal cases (66.7% vs. 31.0% p=0.002). Malaria co-infection was uncommon with 2.5%,
202 3/114 having a positive Malaria RDT on admission.

203

204 **Risk factors for mortality**

205 In unadjusted analyses, the strongest risk factors for mortality were RIFLE-3 AKI (OR 19.7, 95%CI 6.7-57.4,
206 vs. no AKI or RIFLE-1-2 AKI, p<0.001), severely raised AST (OR 16.7, 95%CI 3.7-76.5, vs. not severely raised
207 AST, p<0.001), high haematocrit (OR 13.4, 95%CI 2.7-66.7, vs. normal, p=0.002), low EBOV RT-PCR Ct (OR
208 11.9, 95%CI 4.7-30.1, vs. high Ct, p<0.001), hyperkalaemia (OR 11.1, 95%CI 2.7-45.7, vs. normal potassium,
209 p=0.001), CRP >100mg/dl (OR 9.1, 95%CI 3.1-27.1, vs. CRP ≤100, p<0.001) and granulocytosis (OR 8.7,
210 95%CI 2.9-26.5, vs. normal granulocytes, p<0.001).

211

212 Although hyperkalaemia appeared to be associated with RIFLE-3 AKI, both remained associated with
213 mortality in bivariate analyses (p<0.001). Similarly, haemoglobin and haematocrit were associated with
214 each other, however haematocrit remained strongly associated with mortality after adjusting for
215 haemoglobin (OR 26.9, 95%CI 2.5-289.3). CRP remained strongly associated with mortality (OR 16.5, 95%CI
216 3.8-71.2), even after adjustment for granulocytosis.

217

218 Multivariate analysis was undertaken using variables associated with mortality *a priori* (age, gender, RT-PCR
219 Ct) or in univariate/bivariate analysis. Age was fitted as a continuous variable. Hyperkalaemia, CRP and
220 granulocytosis appeared to become protective due to collinearity and were removed to improve stability.
221 Hematocrit was removed because it had no effect. No interaction terms contributed to the model. The final
222 model is shown in Table 4. The strongest independent risk factors for mortality were low EBOV RT-PCR Ct
223 (OR 6.7, p=0.013, 95% CI 1.5-30.1) and RIFLE-3 AKI (OR 5.8, p=0.033, 95% CI 1.2-29.6). Disease stage on
224 admission was not associated with mortality after adjustment for other risk factors.

225

226 **Discussion**

227 The natural history of EVD is well characterised with a gastrointestinal stage leading to significant
228 hypovolaemia, systemic hypoperfusion and shock in inadequately fluid-resuscitated patients.⁴ The extent of
229 multi-organ dysfunction syndrome—commonly involving the renal, hepatic, neurological and coagulation
230 systems—varies from mild dysfunction to irreversible organ failure and death, but the pathogenesis of EVD
231 remains poorly understood. Key to improving outcomes is the availability of routine biochemistry and
232 haematological testing. Large observational studies are also required to compare data with animal models
233 and support clinical trials of novel therapeutics.

234

235 The majority of our patients were admitted with stage 2 or 3 disease (74/118), and had high levels of organ
236 dysfunction and associated metabolic abnormalities. Fifty percent (52/104) of cases had AKI, and raised
237 creatinine was associated with mortality, supporting earlier published data.^{6,7} Importantly kidney
238 dysfunction was not limited to later disease stage, supporting the role of IV fluid therapy in early disease.

239

240 AKI is generally attributed to pre-renal causes.^{4,15} However, our results suggest AKI may be multifactorial,
241 given the high prevalence in early disease where dehydration is a less common clinical finding. The role of
242 rhabdomyolysis is unclear and worthy of further study given our almost universal findings of elevated CK
243 (and its association with AKI), and disproportionately elevated AST. However CK was rarely elevated to
244 levels associated with AKI, apart from a discreet number of patients who reached the ceiling of our assay
245 measurement. Subsequent renal injury may also arise due to poor renal perfusion secondary to profound
246 hypovolaemia from gastro-intestinal losses, or viral or secondary bacterial sepsis resulting in acute tubular
247 necrosis.¹⁹ Microvascular damage from disseminated intravascular coagulation may also contribute; raised
248 D-Dimer was a common finding in patients with Sudan Ebolavirus⁶ and autopsy of infected primates
249 reported fibrinous cellular debris in glomerulus.²⁰ Importantly, our data show that EVD-associated AKI can
250 be managed successfully in this setting.

251

252 Hepatocellular inflammation has previously been reported.^{8,9} Our data showed that most patients had
253 elevated ALT/AST levels, which was associated with mortality. Normal bilirubin levels indicated fulminant
254 hepatic failure is not a major feature consistent with the clinical syndrome observed. Elevated CRP and
255 granulocytosis were also associated with mortality, which may reflect secondary bacterial infection,²⁰
256 although all patients were treated with a third-generation cephalosporin from stage 2 of clinical disease.

257

258 The data is the first reported on haematological abnormalities, and show that mortality was associated
259 with higher haemoglobin and haematocrit. This may be a surrogate marker for intravascular fluid depletion,
260 widely believed to be associated with poor outcomes.⁴ Thrombocytopenia was common and occurred in
261 45·2% of patients at presentation, but was rarely severe. It was not possible to measure coagulation in our
262 cohort, and this should be a priority for future research given the frequency and poorly understood nature
263 of haemorrhage in EVD. Semi-quantitative EBOV viral load measurement has been shown to be a useful
264 predictor of mortality^{8,12} and was associated with clinical outcome in our series.

265

266 We report a number of study limitations. The CFR is lower than others have reported.^{7,10,11} While this may
267 be due to a high-standard clinical care, it is possible that there is a survivor bias (i.e. patients with EVD more
268 likely to survive were admitted to this ETC) since only patients confirmed to have Ebola were admitted
269 during the study period, and there were time delays prior to ETC admission. This is supported by the finding

270 that some patients were RT-PCR negative at admission, suggesting that they may have already cleared the
271 virus. Caution should be used in comparing CFRs between settings. The finding that a shorter time from
272 symptom onset to admission was associated with mortality may have been caused by recall bias and
273 survivor bias; symptom onset date was collected from records sent with the patient, which were not always
274 complete. Patients also presented to the ETC at different stages of illness, and had variable levels of
275 treatment in holding centres prior to admission.

276

277 Due to an isolator failure, 24 consecutive patients had no laboratory testing. The significance of this to our
278 results is unclear. A number of the assays (AST, ALT, CK) were limited by their upper limits of detection,
279 potentially underestimating the difference between groups. Additionally, baseline creatinine was estimated
280 based on MDRD scores, which may have over- or under-estimated the prevalence of AKI.

281

282 **Conclusion**

283 Our data show that the provision of routine laboratory support to an ETC provides opportunity for
284 improved understanding of disease pathophysiology, and correlation with clinical disease staging. We
285 demonstrate a previously unreported high prevalence of electrolyte imbalance and organ dysfunction in all
286 stages of EVD. The ability to diagnose and treat these abnormalities at presentation and follow patients'
287 response to therapy is likely to improve survival.

288

289 The most important aspects of supportive care are aggressive management of intravascular volume
290 depletion, correcting electrolyte abnormalities, and preventing the complications of shock.²¹ These are
291 underlying tenets of critical care medicine, which can and should be applied in this setting. Improving the
292 provision of good supportive care including laboratory analysis is essential to further clarify the
293 pathogenesis and pathophysiology of EVD in humans. In parallel to ongoing intervention studies, this will
294 inform evidence-based protocols to improve outcomes for this outbreak and the next.

295

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299

300 **Disclosures**

301 None

302

303 **Author Contribution Statement**

304 **LH, AGW, VS, FT, VK, CH, RC and TF contributed towards study design. LH, AGW, VS, FT, VK, KT, SHM, ET,**

305 **AS, SC, TS, ST, TB and TF contributed towards data collection. AGW, VS, ST and TB contributed towards**
306 **data analysis. LH, AGW, VS and TF drafted the manuscript. All authors contributed towards manuscript**
307 **revision.**
308
309

310

311 **Table 1**

Stage	Clinical Features	Typical Patient	Standard Therapy
1 Early/Mild	Non-specific features. Pyrexia, weakness, lethargy, myalgia, arthritis	Ambulatory, able to compensate for fluid losses via oral intake	Oral Rehydration Solution Symptomatic treatment Zinc / Multivitamins Anti-malarials if RDT positive Targeted electrolyte replacement ⁺ Treatment of hypoglycemia
2 Gastrointestinal Involvement	As above plus: diarrhoea, vomiting and/or abdominal pain	Unable to compensate for fluid losses via oral intake due to emesis or loss of large volumes	<i>As per stage 1, plus:</i> IV fluid therapy (3000-6000ml/24h for adults, guided by fluid and electrolyte balance) IV Ceftriaxone*
3 Complicated	As above plus: hemorrhage, shock, neurological involvement and/or signs of organ failure	Critically ill, usually hypovolaemic, often with confusion and/or seizures, bleeding.	<i>As per stage 1+2, plus:</i> As clinically indicated: Sedation/anti-epileptics Vitamin K Fresh Frozen Plasma [#]

312 RDT rapid malaria diagnostic test; IV intravenous. ⁺ Sodium, potassium, magnesium, calcium and phosphate replaced according to
313 biochemistry results. *Ceftriaxone (2g once per day for adults) was given as an empirical 5 day course in all stage 2 and 3 patients.
314 It was continued for longer or given to stage 1 patients if clinically indicated. # Fresh frozen plasma was given when hemorrhage
315 occurred and when available.
316

317 **Table 1** Clinical staging system for Ebola virus disease used at Kerry Town ETC and subsequent standard
318 clinical management.

		Included in study			No laboratory tests sent
		Survived	Died	Total	
	Total number	77	41	118	32
Gender	Male	37 (48.1)	25 (61.0)	62 (52.5)	10
	Female	40 (51.9)	16 (39.0)	56 (47.5)	22
Age (years)	Mean (sd)	23.2 (13.1)	31.0 (16.2)	25.9 (14.7)	25.1 (18.5)
	0-4	3 (3.9)	0	3 (2.5)	5
	5-14	20 (26.0)	8 (19.5)	28 (23.7)	5
	15-24	20 (26.0)	5 (12.2)	25 (21.2)	4
	25-34	20 (26.0)	11 (26.8)	31 (26.3)	9
	35-44	7 (9.1)	8 (19.5)	15 (12.7)	5
	45-80	7 (9.1)	9 (22.0)	16 (13.6)	4
Time from symptom onset to admission (days)	Mean (sd)	5.3 (3.2)	4.4 (2.9)	5.0 (3.1)	5.6 (2.2)
	1-3	16 (20.8)	13 (31.7)	29 (24.6)	4
	4-6	23 (29.9)	14 (34.1)	37 (31.4)	12
	≥7	14 (18.2)	3 (7.3)	17 (14.4)	7
	Unknown	24 (31.2)	11 (26.8)	35 (29.6)	9
Stage at admission	Stage 1	23 (29.9)	8 (19.5)	31 (26.3)	7
	Stage 2	47 (61.0)	25 (61.0)	72 (61.0)	16
	Stage 3	4 (5.2)	8 (19.5)	12 (10.2)	7
	Unknown	3 (3.9)	0	3 (2.5)	2
Ebola RT-PCR at admission	Positive	62 (80.5)	41 (100.0)	103 (87.3)	30
	Negative	15 (19.5)	0	15 (12.7)	1
	No result	0	0	0	1
Malaria RDT	Positive	1 (1.3)	2 (4.9)	3 (2.5)	1
	Negative	72 (93.5)	39 (95.1)	111 (94.1)	29
	Unknown	4 (5.2)	0	4 (3.4)	2

320 Data are numbers (column %) unless otherwise stated. RT-PCR reverse-transcriptase-polymerase-chain-reaction; RDT rapid malaria
321 diagnostic test.
322

323 **Table 2** Characteristics of patients with confirmed Ebola virus disease admitted to Kerry Town ETC during
324 the study period

Table 3

Haematology					
		Survived	Died	Total	Test
Haemoglobin	Mean g/dL (sd)	13.5 (2.1)	15.5 (2.6)	14.2 (2.5)	p<0.001*
	Anemia n (%)	20/66 (30.3)	5/37 (13.5)	25/103 (24.3)	p=0.057#
Haematocrit	Mean % (sd)	39.4 (6.6)	45.1 (7.5)	41.4 (7.5)	p<0.001*
	Raised, n(%)	2/64 (3.1)	13/36 (36.1)	15/100 (15.0)	p<0.001#
	Low, n(%)	29/64 (45.3)	7/36 (19.4)	36/100 (36.0)	
Platelets	Median x10 ⁹ /L (IQR)	146 (108-219)	197 (145-346)	155 (119-247)	P=0.005 [§]
	Thrombocytopenia, n(%)	36/67 (53.7)	11/37 (29.7)	47/104 (45.2)	p=0.019#
White blood cells	Median x10 ⁹ /L (IQR)	7.9 (4.8-12.4)	15.8 (8.6-21.7)	10.0 (5.2-16.0)	p<0.001 [§]
	Raised, n(%)	21/67 (31.3)	25/37 (67.6)	46/104 (44.2)	p=0.001#
	Low, n(%)	12/67 (17.7)	5/37 (13.5)	17/104 (16.4)	
Lymphocytes	Median x10 ⁹ /L (IQR)	2.2 (1.5-3.7)	4.2 (2.2-6.6)	2.6 (1.6-4.4)	p<0.001 [§]
	Raised, n(%)	19/67 (28.4)	24/37 (64.9)	43/104 (41.4)	p=0.001#
	Low, n(%)	7/67 (10.4)	1/37 (2.7)	8/104 (7.7)	
Granulocytes	Median x10 ⁹ /L (IQR)	4.3 (2.5-8.0)	11.5 (4.9-14.0)	5.7 (2.8-11.0)	p=0.001 [§]
	Raised, n(%)	19/67 (28.4)	25/37 (67.6)	44/104 (42.3)	p<0.001#
	Low, n(%)	15/67 (22.4)	7/37 (18.9)	22/104 (21.2)	
Viral Load					
RT-PCR Cycle time	Mean n (sd)*	23.4 (4.3), 60	18.3 (2.7), 39	21.4 (4.5), 99	p<0.001*
	Low, n(%)	16/73 (21.9)	30/39 (76.9)	46/112 (41.1)	p<0.001#
Biochemistry					
Creatinine	Median μmol/L (IQR)	90 (58-161)	467 (225-754)	121 (65-392)	P<0.001 [§]
	RIFLE-1, n(%)	5/72 (6.9)	0/32	5/104 (4.8)	p<0.001#
	RIFLE-2, n(%)	8/72 (11.1)	0/32	8/104 (7.7)	
	RIFLE 3, n(%)	13/72 (18.1)	26/32 (81.3)	39/104 (37.5)	

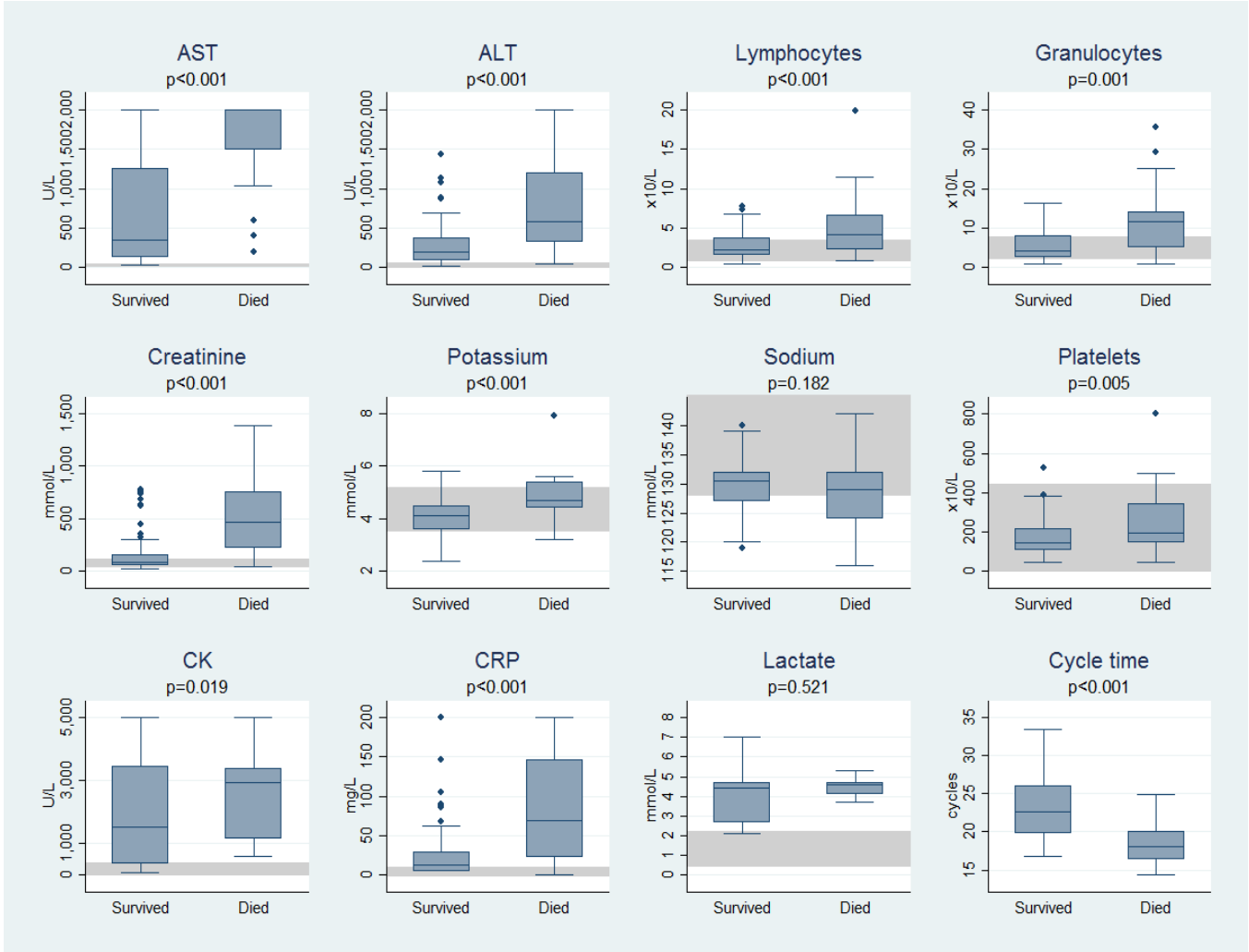
Potassium	Mean mmol/L (sd)	4.0 (0.7)	4.8 (0.9)	4.2 (0.9)	p<0.001*
	Raised, n(%)	3/69 (4.4)	10/28 (35.7)	13/97 (13.4)	p<0.001#
	Low, n(%)	16/69 (23.2)	3/28 (10.7)	19/97 (19.6)	
Sodium	Mean mmol/L (sd)	129.8 (4.6)	128.5 (5.8)	129.4 (5.1)	p=0.182*
	Low, n(%)	22/76 (30.0)	14/37 (37.8)	36/113 (31.9)	p=0.341#
Lactate	Mean mmol/L (sd)	4.0 (1.4)	4.5 (0.6)	4.2 (1.2)	p=0.521*
	Raised, n(%)	11/12 (91.7)	5/5 (100.0)	16/17 (94.1)	p=0.506#
Total dissolved CO₂	Median mmol/L (IQR)	22 (17-28)	17 (11-18)	20 (15-23)	P=0.035 [§]
	Low, n(%)	3/12 (25.0)	4/6 (66.7)	7/18 (38.9)	p=0.087#
Liver function tests					
Alanine transaminase (ALT)	Median IU/L (IQR)	192 (86-371)	577 (314-1195)	253 (121-594)	P<0.001 [§]
	High, n(%)	21/68 (30.9)	16/33 (48.5)	37/101 (36.6)	p<0.001#
	Very high, n(%)	5/68 (7.4)	11/33 (33.3)	16/101 (15.8)	
Aspartate transaminase (AST)	Median IU/L (IQR)	348 (129-1254)	>2000 (1491- >2000)	867 (168- >2000)	P<0.001 [§]
	High, n(%)	11/64 (17.2)	2/28 (7.1)	13/92 (14.1)	p<0.001#
	Very high, n(%)	28/64 (43.8)	26/28 (92.9)	54/92 (58.7)	
AST:ALT ratio	Median (IQR), n	2.2 (1.4-3.3)	3.1 (1.6-3.5)	2.4 (1.4-3.4)	p=0.259 [§]
Creatinine kinase	Median IU/L (IQR), n	1519 (367-3454)	2938 (1137-3400)	1949 (589-3400)	P=0.019 [§]
	High, n(%)	51/68 (75.0)	32/32 (100.0)	83/100 (83.0)	p=0.002#
C-reactive protein	Median mg/L (IQR)	12.9 (5.0-29.4)	69.5 (22.5-147.0)	21.4 (6.0-77.0)	P<0.001 [§]
	High, n(%)	6/68 (8.8)	15/32 (46.9)	21/100 (21.0)	p<0.001#

All data are numbers (column %) unless otherwise stated. *median only presented for RT-PCR results that were positive. * denotes p-value from t-test, #denotes p-value from χ^2 test, [§]denotes p-value from Wilcoxon rank-sum. Definitions are as follows; RT-PCR - reverse-transcriptase-polymerase-chain-reaction, anemia - as per WHO definitions,²² thrombocytopenia <150 x 10⁹/L, raised white cell count >11 x10⁹/L, low white cell count <4 x10⁹/L, raised lymphocytes >3.2 x10⁹/L, low lymphocytes <1 x10⁹/L, raised granulocytes >7.5 x10⁹/L, low granulocytes <2.5 x10⁹/L, low RT-PCR Cycle time <20 cycles, RIFLE-1 AKI 1.5-2 x baseline creatinine, RIFLE 2 AKI 2-3 x baseline creatinine, RIFLE-3 AKI >3 x baseline creatinine, raised potassium >5.1 mmol/L, low potassium <3.6mmol/l, raised Lactate >2.1 mmol/l, low total dissolved CO₂ <18 IU/L, high ALT >240 - ≤720 IU/L, very high ALT >720 IU/L, high AST >175 - ≤525 IU/L, very high AST >525 IU/L, high creatinine kinase >380 U/L and high c-reactive protein >100 mg/l.

Table 3 Laboratory results and abnormalities in patients admitted to Kerry Town ETC with confirmed Ebola

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327 **Figure 1**



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ALT alanine transaminase; AST aspartate transaminase; CK creatinine kinase; CRP C-reactive protein; Cycle time is Ebolavirus reverse-transcriptase-polymerase-chain reaction cycle time. P-values are from t-tests (potassium and sodium) and Wilcoxon rank-sum tests (all others). Shaded area indicates normal range for the UK based population.

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Figure 1 Box plots of laboratory results from patients admitted to Kerry Town ETC; results are presented by outcome.

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336 **Table 4**

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Female Gender	0.59 (0.27-1.28)	0.182	0.33 (0.07-1.63)	0.174
Age	1.04 (1.01-1.07)	0.008	1.01 (0.95-1.06)	0.819
Disease stage	2.16 (1.08-4.32)	0.029	1.40 (0.41-4.84)	0.593
RT-PCR Cycle threshold <20	11.88 (4.69-30.06)	<0.001	6.72 (1.50-30.07)	0.013
RIFLE-3 AKI	19.67 (6.73-57.43)	<0.001	5.84 (1.15-29.58)	0.033
AST>525 U/L	16.71 (3.65-76.47)	<0.001	6.95 (0.70-68.86)	0.097
Potassium >5.1 mmol/L	11.11 (2.70-45.66)	<0.001	-	
CRP >100mg/dl	9.12 (3.07-27.07)	<0.001	-	
Granulocytes >7.5 x10⁹/L	8.68 (2.85-26.45)	<0.001	-	
High haematocrit	13.41 (2.70-66.67)	0.002	-	

337 OR odds ratio; RT-PCR reverse-transcriptase-polymerase-chain-reaction; AST aspartate transaminase, AKI acute kidney injury. P-
 338 values are from likelihood ratio tests. Age was treated as a continuous variable.
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340 **Table 4** Factors associated with mortality in patients with previously confirmed Ebola virus admitted to

341 Kerry Town ETC

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