

# **Postpartum trend in blood pressure and renal function in women with severe preeclampsia and eclampsia: A prospective cohort-study at Mulago hospital, Kampala, Uganda**

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## 1 **Abstract**

## 2 **Background**

3 Preeclampsia/Eclampsia is a multisystem disorder of pregnancy with kidney involvement. Our  
4 objective was to assess the postpartum trend in blood pressure, renal function and proteinuria  
5 and, to investigate their predictors in Ugandan women with severe preeclampsia and eclampsia.

## 6 **Methods**

7 This was a prospective cohort study that involved 97 women with severe preeclampsia and  
8 Eclampsia, conducted at Mulago National referral hospital from August 2017 to April 2018. The  
9 clinical and laboratory variables were collected from the women on day1, 7, 21 and day 42 after  
10 delivery. Kaplan-Meier Survival analysis, Cox-proportional Regression and Log-Rank tests were  
11 used to compare the baseline and the follow-up variables with changes in blood pressure, renal  
12 function and urine protein.

## 13 **Results.**

14 Most women (93.8%) recovered from hypertension within 6 weeks of childbirth with the mean  
15 time to resolution of 2.49 weeks (95% CI: 2.13-2.82). About 81% of the women recovered their  
16 renal function and the mean time to recovery was 24.54 days (95% CI: 20.14-28.95). Proteinuria  
17 resolved in approximately 84% of the women and the mean time resolution of urine protein of  
18 32.85 days (95% CI: 30.31-35.39). Having multiple pregnancy versus a singleton pregnancy was  
19 associated with persistence of hypertension six weeks after child birth (P-value = 0.013).

## 20 **Conclusion**

21 In this study, the blood pressure and renal function of most women with severe preeclampsia and  
22 eclampsia normalized within six weeks after childbirth. A special interdisciplinary follow up for  
23 patients with preeclampsia/eclampsia by an obstetrician and physician is needed in the  
24 postpartum period to reduce the maternal morbidity and mortality associated with this condition  
25 in our community.

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42 **Keys words**

43 Preeclampsia, Hypertension, Proteinuria, Renal dysfunction, Resolution, Postpartum.

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## 46 **Introduction**

47 Preeclampsia is a multisystem human specific pregnancy disorder characterized by new onset  
48 hypertension and proteinuria after 20 weeks of pregnancy(1). It affects 2-8% of all pregnancies  
49 worldwide and contributes significantly to maternal, fetal and neonatal morbidity and mortality  
50 (2). Preeclampsia with other hypertensive disorders in pregnancy contributed to 14% of maternal  
51 deaths worldwide (3). It is estimated to cause 8% of the severe maternal morbidity in Uganda is  
52 the leading cause of maternal deaths (4). Women with preeclampsia have an increased risk of  
53 renal, cerebrovascular and cardiovascular complications after delivery(5). In low resource  
54 settings, preeclampsia is an important cause acute kidney injury and contributes to one third of  
55 the cases seen in late pregnancy (6). Half of the women with acute kidney injury require dialysis  
56 and when dialysis is not available as is commonly the case in many low resource settings, acute  
57 kidney injury frequently leads to death of the women. Studies show that women recover their  
58 renal function after preeclampsia (7), however, other workers have revealed that women with  
59 preeclampsia are at a 5 to 12-fold increased risk of end-stage renal disease (8) and therefore  
60 require prolonged nephrological follow up. The development of renal disease after preeclampsia  
61 is not clearly understood. The renal injury may be due to extensive endothelial or podocyte  
62 injury (9) seen in women with preeclampsia. This leads to nephron loss and later development of  
63 renal disease.

64 Women with preeclampsia on the other hand are at increased risk of cardiovascular disease  
65 compared to normotensive women. They therefore require long time follow up regarding  
66 hypertension after delivery(10). The mechanisms of developing chronic hypertension is not  
67 clear. However, it may be due organ damage or preeclampsia may be a risk factor for later

68 development chronic hypertension. (1). Studies in Uganda have shown that up to one third of the  
69 women with preeclampsia had persistent hypertension after the puerperium (11, 12). The  
70 predictors for persistent hypertension were participants age (11, 12), gestational age at delivery  
71 and parity of the mother (12).

72 It is therefore important that women with preeclampsia are followed after the puerperium if the  
73 blood pressure and renal dysfunction do not resolve. The purpose of this study therefore was to  
74 evaluate the postpartum trend in blood pressure, renal dysfunction and, proteinuria and to  
75 determine the factors associated with their resolution in women with severe preeclampsia and  
76 Eclampsia in Mulago hospital.

## 78 **Methods**

### 79 **Study design**

80 This was a prospective cohort study conducted from August 2017 to April 2018 in Uganda. This  
81 study was approved by the Mulago hospital ethics committee, the Makerere School of Medicine  
82 Research and Ethics committee and Uganda National Council for Science and Technology.  
83 Written informed consent was obtained from the participants.

### 84 **Setting**

85 This study was conducted at Mulago hospital. Mulago hospital is a national referral hospital for  
86 Uganda and serves as the teaching hospital for Makerere University College of Health Sciences.  
87 Mulago Hospital delivers about 30,000 women per year and offers antenatal and postnatal  
88 services.

### 89 **Study population**

90 The study population consisted of women with severe preeclampsia and eclampsia who delivered  
91 at Mulago hospital during the study period. Women with a known history of hypertension,  
92 diabetes mellitus and kidney disease were excluded from the study.

93 Preeclampsia was defined according to the classification by the Working group of National High  
94 blood pressure Education program (2000) and the American College of Obstetricians and  
95 Gynecologists (2013) (13). Under this classification, hypertension was defined as a systolic  
96 blood pressure of  $\geq 140$ mmHg and/or diastolic blood pressure of  $\geq 90$ mmHg on 2 occasions at



97 least 4 hours or more apart. Proteinuria was defined as urine protein of  $\geq 300\text{mg}/24\text{h}$  urine  
98 collection or protein/creatinine ratio of  $\geq 0.3$  or a dipstick reading of  $\geq 2+$ . Preeclampsia was  
99 taken as hypertension with proteinuria after 20 weeks gestation.

100 A woman with preeclampsia was taken to have severe preeclampsia if she had BP of  $\geq 160$   
101 mmHg systolic or  $\geq 110$  mmHg diastolic, severe headache or visual disturbances,  
102 thrombocytopenia of  $\leq 100,000/\mu\text{L}$ , aspartate transaminase or alanine transaminase  $> 2$ times the  
103 upper limit with severe epigastric or upper quadrant pain, pulmonary edema or serum creatinine  
104  $\geq 1.1\text{mg}/\text{dL}$ . A woman with preeclampsia was taken to have eclampsia if she developed a  
105 convulsion that could not be attributed to any other cause (14).

## 106 **Sample size**

107 We assumed that the persistence of hypertension would be 42.6% as was found in a study by  
108 Kaze et.al (15) and parity as a biggest risk factor for preeclampsia with an odds ratio of 3.71 as  
109 was found in a study in Mulago hospital (16). With these estimates a sample size of 97  
110 participants would be sufficient with power of 80% at confidence level of 95% taking in account  
111 of the anticipated loss to follow up of 5%.

## 112 **Study procedures**

113 The research assistants who were qualified midwives identified women with severe preeclampsia  
114 and eclampsia from the labour ward and the high dependence unit of the hospital. They  
115 approached the attendants of the women and gave them information about the study. The  
116 attendants were conducted through an informed consent procedure and gave a written informed  
117 consent. The women later gave informed consent when they improved. Information was obtained

118 from the attendants and from the abstraction of the charts and later verified from the women  
119 when they improved. The eligible participants were recruited consecutively until the required  
120 sample size was achieved. The information from the women was collected using an interviewer-  
121 administered questionnaire, participants' examination, and biochemical investigations. Urine was  
122 collected from the women for urine protein estimation and blood was drawn for serum creatinine  
123 measurement.

## 124 **Follow up**

125 The women were followed for 6 weeks after delivery. The women were reviewed on day 1,7,21  
126 and day 42 by the research team. During the review the women were asked about their health and  
127 a focused history and examination were done using case record form. The blood pressure was  
128 measured, blood was drawn from the women for measurement of serum creatinine and urine for  
129 estimation of urine protein. For renal function, a software package was used to estimate the  
130 glomerular filtration rate using current serum creatinine, patient race, gender and age of the  
131 participant (17). The MDRD calculator was used for determining and classifying the estimated  
132 glomerular filtration <https://patient.info/doctor/estimated-glomerular-filtration-rate-gfr-calculator>

## 133 **Outcomes**

134 The primary outcome was time to resolution of the blood pressure. Secondary outcomes were  
135 time to recovery of renal function and disappearance of proteinuria. The blood pressure was  
136 considered normal when it was less than 140/90 mmHg without any antihypertensive  
137 medications for at least one week.

138 Serum creatinine level and estimated glomerular filtration were measured at every visit and were  
139 considered normal when the estimated glomerular filtration was  $\geq 90$  mL/min/1.73 m<sup>2</sup>

140 Urine protein was considered to have returned to normal if the measurement of spot urine by  
141 dipstick was less than 30mg/dl.

## 142 **Data analysis**

143 The data were coded and double entered using the Epi-data Version 3.1 and analyzed with  
144 STATA version 12. Counts, means, median, percentage and cumulative percentage were used to  
145 report the results. Survival analysis with Kaplan-Meier was used to determine time to resolution  
146 of hypertension, renal dysfunction and urine protein. Cox- proportional regression and Log rank  
147 test were used to determine association of participant variables with time-to resolution of  
148 hypertension, renal dysfunction and urine protein. Association was considered statistically  
149 significant if it had a P-value of less than 0.05.

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## 152 **Results**

153 In this study 97 women with severe preeclampsia/Eclampsia were followed up for 6 weeks after  
154 childbirth. The time to resolution of hypertension, renal function and proteinuria, and the  
155 associated factors were determined.

156 All the 97 participants had hypertension, 20 were censored: 2 women died, 12 were lost to  
157 follow-up by the third visit, and 6 had persistent hypertension by the end of this study.

158 Forty seven participants had abnormal renal functions, 10 were censored: 9 women had  
159 persistent renal dysfunction by the end of the study and 1 woman was lost follow up.

160 Finally, 92 had proteinuria: 29 were censored because 15 women had persistent proteinuria by  
161 the end of the study and 14 women were lost to follow up (Fig 1).

162 The mean age of the participants was  $26.6\pm 5.4$  years, mean gestation age was  $35.9\pm 4.0$  weeks  
163 and a modal parity was 2 with a range of 1-6.

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174 **Figure 1: Flow chat of 97 participants with severe preeclampsia and eclampsia**

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178 The mean time to resolution of hypertension was 2.49 weeks (CI: 2.13-2.84). The blood  
179 pressure decreased over the 6 weeks period of follow-up. Only 6 women (6.2%) had persistent  
180 hypertension 6 weeks after delivery (Fig 2). The decrease of blood pressure was not affected by  
181 the time of onset of preeclampsia ( $p=0.426$ ), mode of delivery ( $p=0.891$ ) and the parity of the  
182 woman ( $p=0.139$ ).

183 After controlling for other variables, having multiple pregnancy versus singleton pregnancy was  
184 significantly associated with persistence of hypertension 6 weeks after delivery ( $p$  value =0.013)  
185 (Fig 3). Other factors like time of development of preeclampsia, parity and mode of delivery  
186 were not associated with persistence of hypertension 6 weeks after childbirth.

187 The mean time for the recovery of the renal function was 24.5 days (95% CI: 20.14-28.95). The  
188 renal function improved during the six weeks of follow up and only 9 (19.1%) women had  
189 persistent renal dysfunction at 6 weeks follow-up (Fig 4). There recovery of the renal function  
190 was not associated with mode of delivery of the patient ( $p=0.256$ ), onset of preeclampsia

191 (p=0.180), parity of the patient (p=0.709) and whether the mother delivered single or multiple  
192 pregnancy (p=0.147).

193 The mean time for the resolution of proteinuria was 32.9 days (95% CI: 30.3-35.4). Urine protein  
194 decreased over the six week follow-up and 15 (16.3%) women had persistent proteinuria by the  
195 end of the study (Fig 5). The resolution of proteinuria was not associated with mode of delivery  
196 (p=0.267), onset of preeclampsia (p=0.660), parity (p=0.135) and single versus multiple  
197 pregnancy (p=0.075).

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199 **Figure 2: Kaplan-Meier curve of time to resolution of hypertension in women with**  
200 **preeclampsia and eclampsia**

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204 **Figure 3: Kaplan-Meier curve for time to resolution of hypertension in women with single**  
205 **versus multiple pregnancy**

206 Women with multiple pregnancy were more likely to have persistence of hypertension when  
207 compared women with singleton pregnancy (p=0.013)

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218 **Figure 4: Kaplan-Meier curve of time to resolution of renal dysfunction in women with**  
219 **severe preeclampsia and eclampsia**

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228 **Figure 5: Kaplan-Meier curve of time to resolution of urine protein in women with severe**  
229 **preeclampsia and eclampsia**

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## 233 **Discussion**

234 This was a prospective cohort study in which 97 women with severe preeclampsia and eclampsia  
235 were followed after childbirth. In this study, 93.8% (91/97) of the women recovered from  
236 hypertension within 42 days after childbirth. This is in agreement with a study by Wei et al (18)  
237 in which 90% of their patients recovered from hypertension within 60 days after childbirth and  
238 Mikami et al (19) in which 90% of the women required 77 days to recover from hypertension.  
239 We considered the blood pressure to be normal if it was less than 140/90mmHg without using  
240 antihypertensive treatment for at least one week. In our study most women had an earlier  
241 recovery than the women in these other studies by Wei et al (18) and Mikami et al (19). This was  
242 probably because most mothers in our study had late onset preeclampsia at a gestational age of  
243  $35.9\pm 4.0$  weeks. Many studies have shown an association of a late onset of preeclampsia with  
244 early recovery of hypertension (11, 19). In our study 6 (6/97, 6.2%) women had persistent  
245 hypertension 6 weeks after delivery. This calls for prolonged follow up of women with  
246 hypertensive disease in pregnancy. Indeed the Society of Obstetricians and Gynaecologists of  
247 Canada clinical practice guidelines recommends follow up after six weeks to ascertain recovery  
248 from the effects of pregnancy and childbirth and ensure ongoing care with physicians or  
249 nephrologists(20). It has been shown that glomerular endothelial injury due to preeclampsia  
250 recovers within four weeks after delivery (21). Therefore women with persistent hypertension six  
251 weeks after delivery need adequate follow up to manage the underlying causes.

252 In this study, there was a statistically significant difference in the time to resolution of  
253 hypertension between singleton pregnancy versus multiple pregnancy: the time to resolution of  
254 hypertension was significantly shorter in singleton pregnancy ( $35.3\pm 18.6$  days) when compared

255 to multiple pregnancy (43.5±31.4 days). This finding disagrees with what Mikami et. al. (19)  
256 found in their study. The normalization of blood pressure was significantly longer in singleton  
257 pregnancy than multiple pregnancy.

258 In this study, 47(47/97, 48.5%) participants had renal dysfunction after delivery: 24 women  
259 (24/47, 51.1%) were in stage 2, 18/47(38.3%) in stage 3 and 4/47(8.5%) in stage 4 of chronic  
260 kidney disease. At 6 weeks postpartum, 38 women (38/47, 80.9 %) resolved and 9(9/47, 19.1%)  
261 had persistent renal dysfunction: 6 in stage 2 and 3 in stage 3 chronic renal disease. The  
262 prevalence of renal dysfunction was higher than 24.1% that was found by Kaze et al in  
263 Cameroonian women (15) and 35.3% that was found by Prakash et al (6) in Indian women.  
264 Renal dysfunction is due glomerular endotheliosis which occurs in women with  
265 preeclampsia/eclampsia. Other studies have reported that resolution of the renal lesions may take  
266 up to two years (21). In our study, 18.6% of the women had persistent renal dysfunction six  
267 weeks after delivery. This is a reflection of the persistent effect of endothelial damage seen in  
268 preeclampsia(22). Most of these women are expected to recover within two years after delivery  
269 as this does not indicate chronic disease (23). However, this calls for prolonged follow up with a  
270 nephrologist.

271 We observed persistence of proteinuria of 16.3% at six weeks after delivery. This was lower than  
272 what was found in other studies (15, 19). Proteinuria is due endothelial dysfunction which plays  
273 a central role in the pathogenesis of preeclampsia (24). It has been shown that circulating soluble  
274 fms like tyrosine kinase-1 (sFlt-1) are elevated and these bind circulating vascular endothelial  
275 growth factor (VEGF). These have an association with glomerular endotheliosis and  
276 proteinuria(25). The resolution of proteinuria may echo the endothelial recovery seen after  
277 preeclampsia (26). These results may suggest that the time to resolution of proteinuria may be

278 dependent on the degree and duration of endothelial cell injury. We expect most of the mothers  
279 with proteinuria to recover within two years as has been found in others studies(27). Proteinuria  
280 at six weeks does not indicate chronic disease. It most probably a temporary effect of endothelial  
281 damage seen in preeclampsia and more invasive investigations should be delayed until two years  
282 after delivery.

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## 292 **Conclusion**

293 In this study, 16.3% participants had persistent proteinuria, 6% had persistent hypertension and  
294 19.6% had persistent renal function six weeks after delivery. Special interdisciplinary follow up  
295 of the patients with preeclampsia/eclampsia by an obstetrician and a physician after delivery is  
296 required to reduce maternal morbidity and mortality associated with preeclampsia/eclampsia in  
297 our community.

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306 and our research team.

## 307 **Author Contributions**

308 Conceived and designed the study: MK, PK, JB, JW, MWM. Participated in data collection and  
309 analysis: MK, PK, JB, JW, MWM, Interpreted the data and drafted the manuscript: MK, PK, JB,  
310 JW, MWM Reviewed and approved the final manuscript: MK, PK, JB, JW, MWM

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Total number recruited

N=97 with Preeclampsia/Eclampsia  
97 women had hypertension

77 achieved the event

20 were censored

Died =02

Persistent: 6

Lost follow up: 12

47 had renal dysfunction

92 had urine protein

37 achieved the event

10 were censored

29 were censored

63 achieved the event

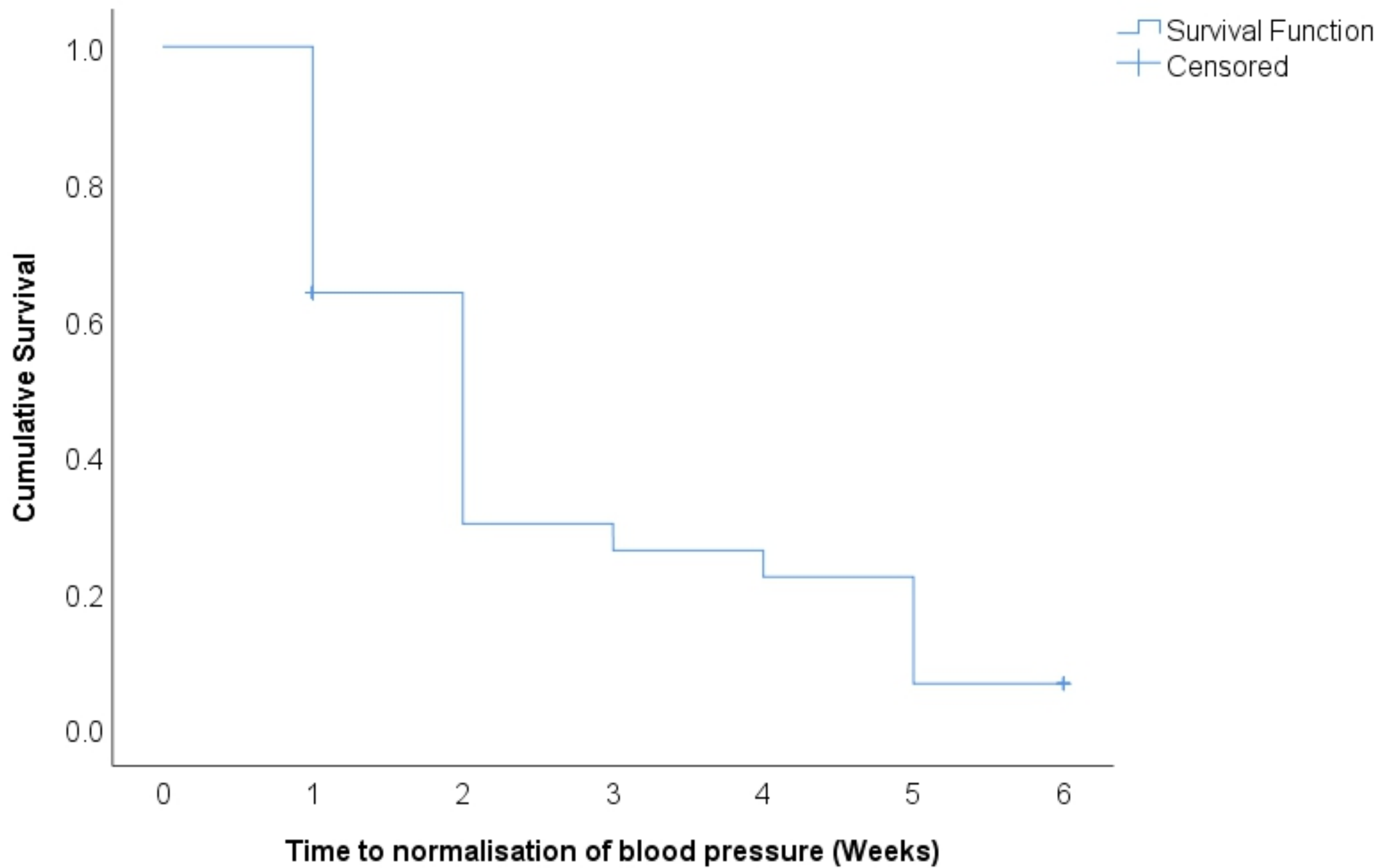
Lost follow up: 1

Persistent: 9

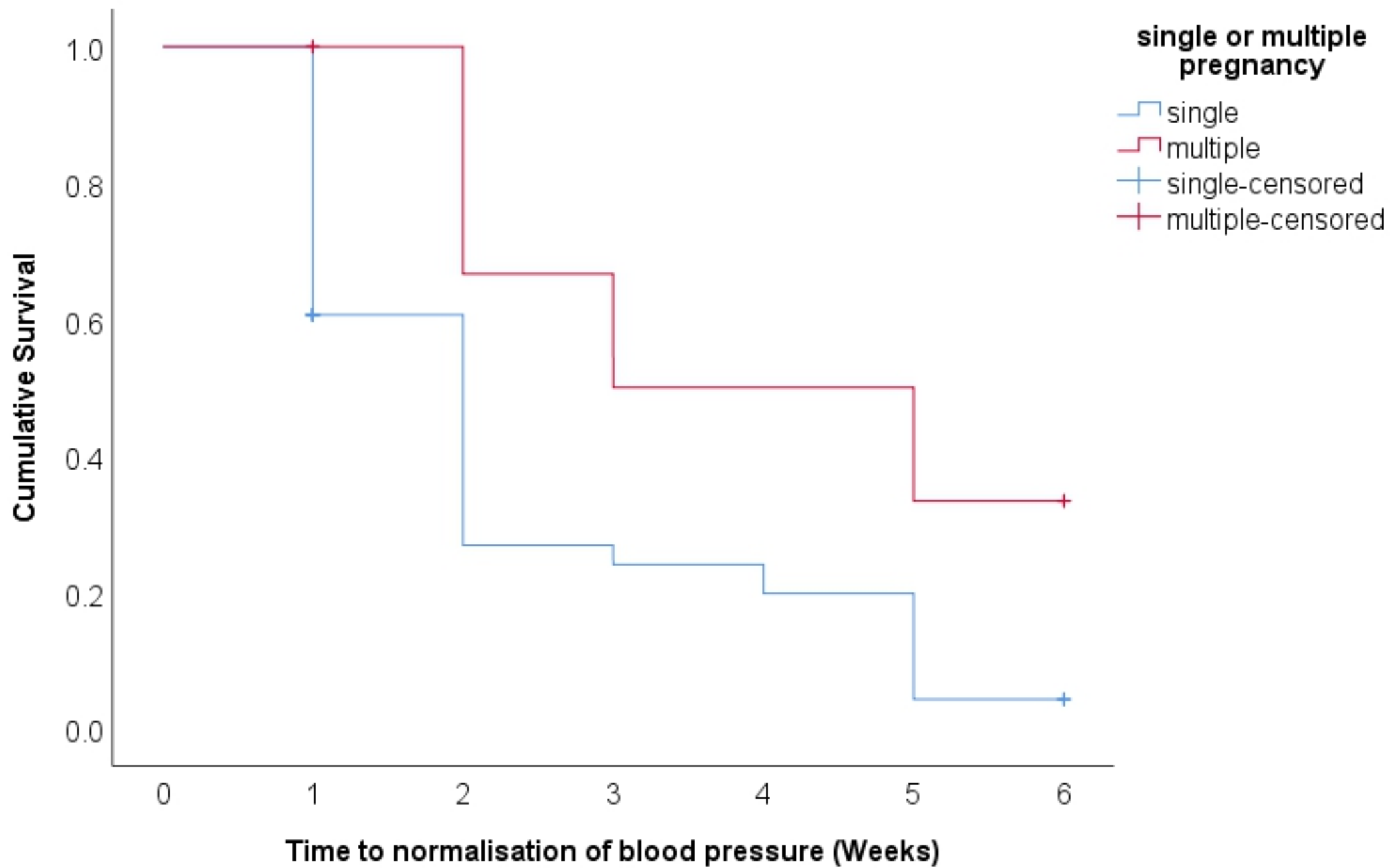
Lost follow up: 14

Persistent: 15

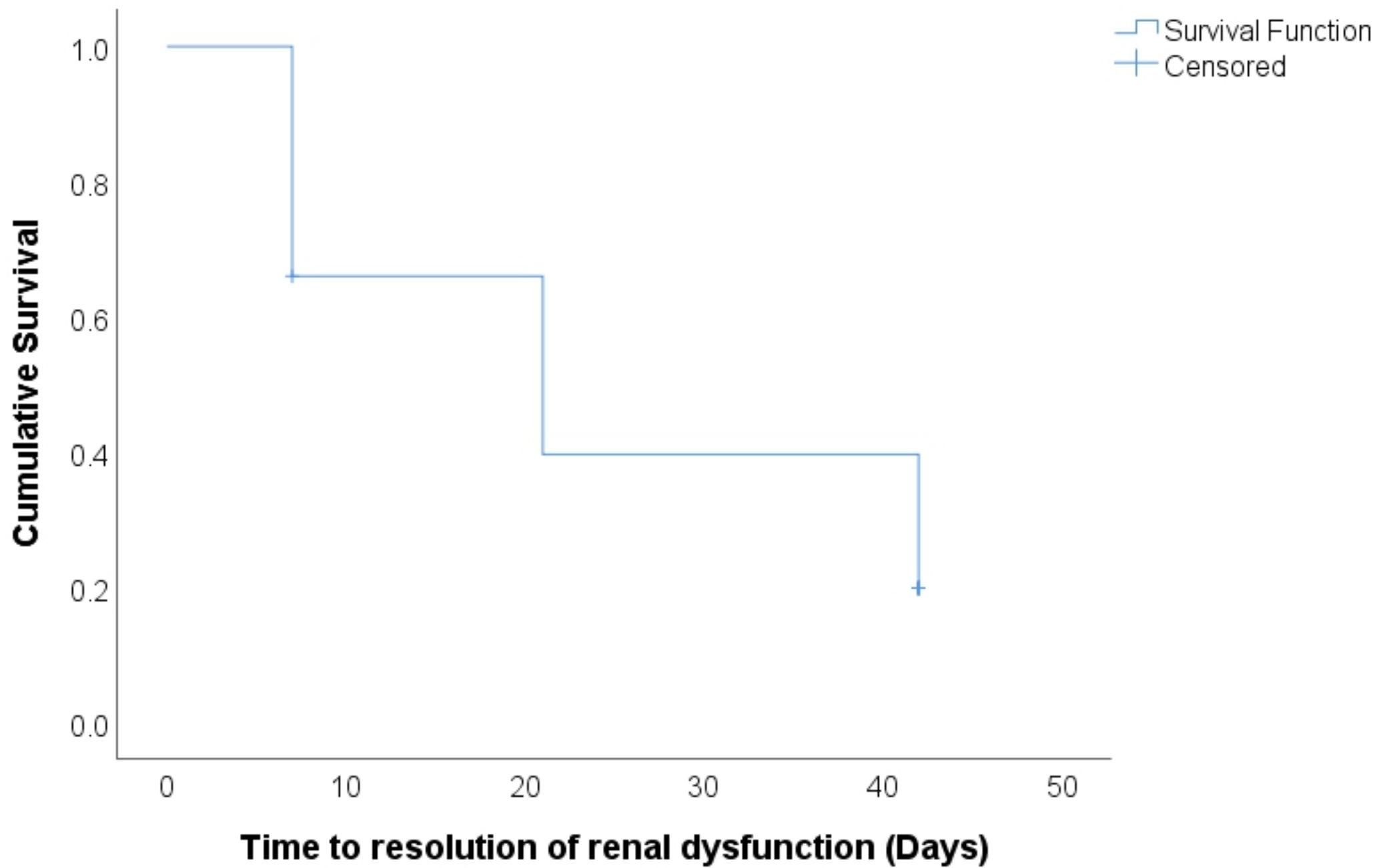
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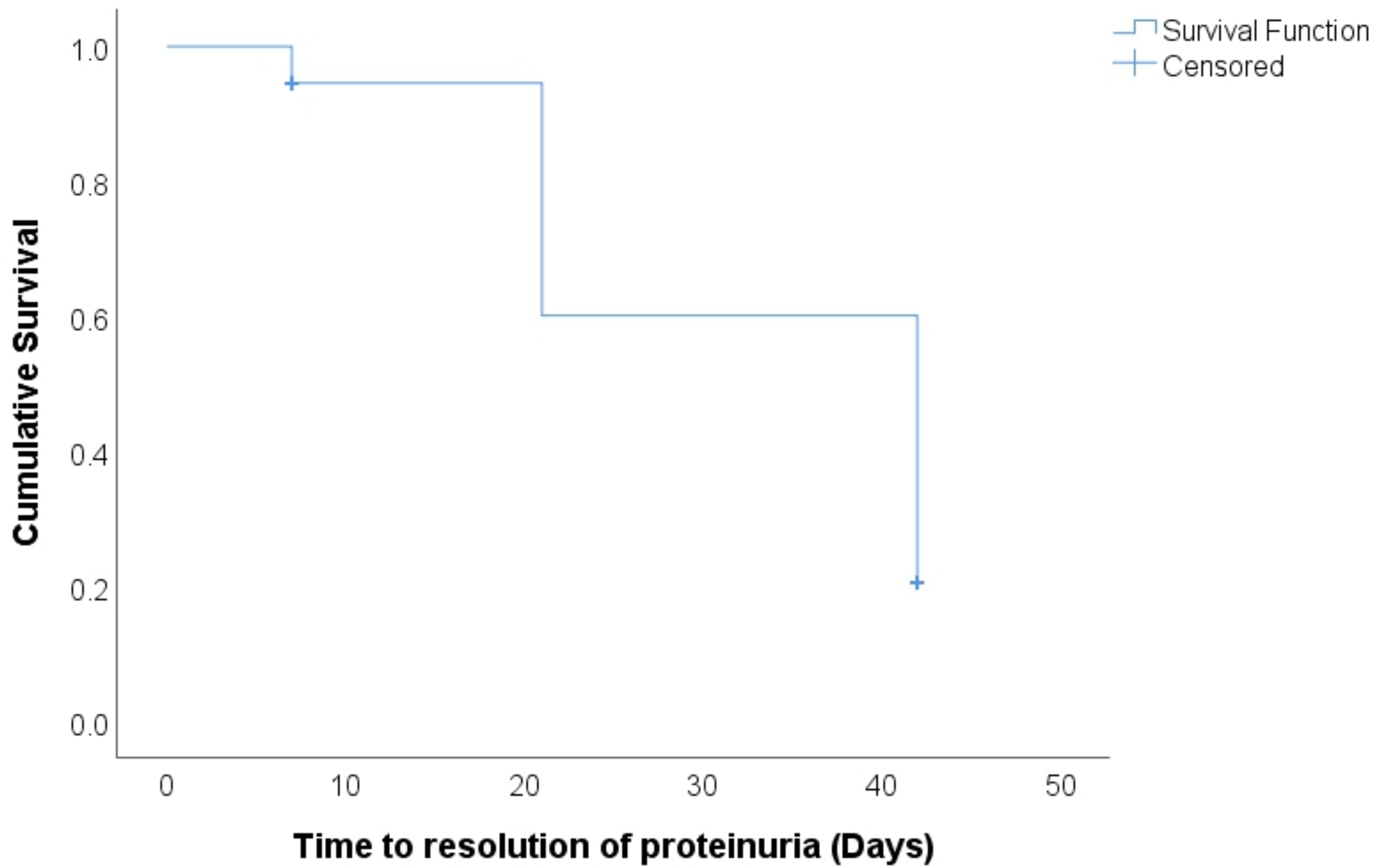
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