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# Effect of post-operative goal-directed fluid therapy (GDFT) on organ function after orthotopic liver transplantation: Secondary outcome analysis of the COLT randomised control trial

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1 **Effect of post-operative Goal-Directed Fluid Therapy (GDFT)**  
2 **on organ function after orthotopic liver transplantation:**  
3 **secondary outcome analysis of the COLT trial**

4 **Abstract**

5 **Background:** Goal-directed fluid therapy (GDFT) has been shown to reduce the complications  
6 following a variety of major surgical procedures, possibly mediated by improved organ perfusion and  
7 function. We have shown that it is feasible to randomise patients to GDFT or standard fluid  
8 management following liver transplant in the cardiac-output optimisation following liver  
9 transplantation (COLT) trial. The current study compares end organ function in patients from the  
10 COLT trial who received GDFT in comparison to those receiving standard care (SC) following liver  
11 transplant.

12 **Methods:** Adult patients with liver cirrhosis undergoing liver transplantation were randomised to  
13 GDFT or SC for the first 12 hours following surgery as detailed in a published trial protocol. GDFT  
14 protocol was based on stroke-volume (SV) optimisation using 250ml crystalloid boluses. Total fluid  
15 administration and time to extubation were recorded. Hourly SV and cardiac output (CO) readings  
16 were recorded from the non-invasive cardiac output monitoring (NICOM) device in both groups.  
17 Pulmonary function was assessed by arterial blood gas (ABG) and ventilatory parameters. Lung  
18 injury was assessed using PaO<sub>2</sub>:FiO<sub>2</sub> ratios and calculated pulmonary compliance. The KDIGO score  
19 was used for determining acute kidney injury. Renal and liver graft function were assessed during  
20 the post-operative period and at 3 months and 1-year.

21 **Results:** 60 patients were randomised to GDFT (n=30) or SC (n=30). All patients completed the 12h  
22 intervention period. GDFT group received a significantly higher total volume of fluid during the 12h  
23 trial intervention period (GDFT 5317 (2335) vs. SC 3807 (1345) ml, p=0.003); in particular crystalloids  
24 (GDFT 3968 (2073) vs. SC 2510 (1027) ml, p=0.002). There was no evidence of significant difference  
25 between the groups in SV or CO during the assessment periods. Time to extubation, PaO<sub>2</sub>: FiO<sub>2</sub>

26 ratios, pulmonary compliance, ventilatory or blood gas measurements were similar in both groups.  
27 There was a significant rise in serum creatinine on from baseline (77 $\mu$ mol/L) compared to first  
28 (87 $\mu$ mol/L, p=0.039) and second (107 $\mu$ mol/L, p=0.001) post-operative days. There was no difference  
29 between GDFT and SC in the highest KDIGO scores for the first 7 days post-LT. At 1-year follow-  
30 up, there was no difference in need for renal replacement therapy or graft function.

31 **Conclusions:** In this randomised trial of fluid therapy post liver transplant, GDFT was associated  
32 with an increased volume of crystalloids administered but did not alter early post-operative pulmonary  
33 or renal function when compared with standard care.

34

35 **1. Introduction**

36 Significant improvements in surgical technique, anaesthesia, critical care and immunosuppression  
37 have made liver transplantation (LT) a safe treatment for end-stage liver disease with 1-year survival  
38 of 94% in the United Kingdom (1). However, post-operative complications are common with rates of  
39 up to 50% with substantial associated patient morbidity and associated healthcare costs (2). Goal-  
40 directed fluid therapy (GDFT) guided by haemodynamic measures has been shown to reduce post-  
41 operative complications in patients undergoing major abdominal surgery (3). The postulated  
42 mechanism is that GDFT improves organ perfusion, oxygenation and hence end-organ function (4).  
43 However, there are major metabolic and haemodynamic differences between patients having major  
44 general surgery and cirrhotic patients undergoing LT. We cannot therefore assume GDFT will be  
45 beneficial to these patients.

46 Cirrhosis results in portal hypertension and activation of vasoactive substances such as nitric oxide  
47 which reduce the systemic vascular resistance and lead to altered systemic haemodynamics (5).  
48 Consequently, cirrhotic patients have a high cardiac output and a reduced central blood volume at  
49 baseline. An additional factor is that cirrhotic cardiomyopathy is present in up to 30% of patients  
50 undergoing LT (6). This, coupled with a degree of autonomic dysfunction especially in those who  
51 have alcohol related cirrhosis means that traditional measures of assessment of fluid requirements  
52 such as blood pressure, heart rate and urine output are unreliable (5). Furthermore, LT surgery with  
53 major blood loss requiring transfusion further complicates the haemodynamic alterations which follow  
54 the partial or complete cross-clamping of the inferior vena cava during implantation of the graft. There  
55 is also a significant surgical stress response which is exacerbated by reperfusion of the donor organ  
56 due to ischaemia reperfusion injury (7).

57 Hence, in cirrhotic patients undergoing LT it is difficult to ensure they remain euvoletic, although  
58 this may be vital to both the perfusion of the graft as well as other organs. It has been shown that  
59 excessive or inappropriate perioperative fluid volume can have a detrimental impact on early  
60 pulmonary and renal function after LT (8,9). There is tremendous variability in GDFT protocols related

61 to the method of assessment of fluid responsiveness and fluid resuscitation end-goals for achieving  
62 a euvolemic state as well as the type of fluid administered with or without pharmacological adjuncts.  
63 The COLT trial has demonstrated that it is feasible and safe to randomise patients post liver  
64 transplant to GDFT vs. SC using a simple stroke volume (SV) optimisation protocol (10). This trial  
65 was not powered to address efficacy. The study provided an opportunity to evaluate organ end-organ  
66 function in cirrhotic patients randomly allocated to GDFT or SC for the first 12 hours following LT.  
67 The aim of this study is to report the effect of post-operative GDFT on post-operative end-organ  
68 function in patients with liver cirrhosis undergoing LT.

69

## 70 **2. Patients and Methods**

### 71 *2.1 Study setting and patients*

72 The clinical trial was conducted according to the previously published protocol (11). Adult patients  
73 (age 18 to 80 years) with a diagnosis of liver cirrhosis listed for LT at the Royal Free London NHS  
74 Foundation Hospital Trust, were invited to participate in the trial. The exclusion criteria were patients  
75 who were unable to consent, aged less than 18 or greater than 80 years, body weight less than 40kg,  
76 re-transplantation, fulminant hepatic failure, emergency surgery, non-cirrhotic liver disease,  
77 prisoners, those who had learning disabilities or lacked capacity or refused to consent.

78

### 79 *2.2 Study design and randomisation*

80 A prospective single centre randomised controlled trial of GDFT vs. SC was conducted according to  
81 the SPIRIT guidelines (12). All eligible patients undergoing liver transplant were provided with a  
82 COLT trial patient information sheet and consented for by a trial nursing staff or LT co-ordinator  
83 trained in Good Medical Practice (GCP). Eligible patients were randomised to either GDFT or SC  
84 immediately after liver transplantation at the time of admission to the intensive care unit (ICU) using  
85 a commercially available clinical randomisation service ([www.sealedenvelope.com](http://www.sealedenvelope.com)). Patients were  
86 randomised by the trial nurses on a 1:1 basis stratified by donor type (deceased after cardiac death

87 (DCD) or deceased after brain death (DBD)) to achieve approximate balance between the two groups  
88 in this characteristic.

89

### 90 *2.3 Intervention and blinding*

91 Both the intervention and control groups had continuous haemodynamic monitoring via a FloTrac™  
92 non-invasive pulse wave contour analysis sensor (EV1000, Edwards Life Sciences, USA) for the first  
93 12 hours post transplantation. Patients returned to the ICU mechanically ventilated and were weaned  
94 off sedation with a plan for extubation on the first post-operative day. The FloTrac™ readings were  
95 available for the trial nurse delivering the GDFT protocol. The ICU clinicians and the transplant clinical  
96 team were blinded to the results of the FloTrac™ in both the GDFT and the SC control groups.

97 GDFT was delivered by a trial nurse specialist using an hourly SV optimisation algorithm (figure 1)  
98 for the first 12h of ICU admission. The control group received standard post-operative fluid therapy  
99 as deemed appropriate by the treating clinicians without the use of the FloTrac™ (although a FloTrac  
100 was used by the research team in this group, to measure – but not act on – haemodynamic variables).

101

### 102 *2.4 Clinical outcome measures*

103 The COLT feasibility study demonstrated that it was possible to randomise patients to GDFT or SC  
104 following LT and that GDFT was safe to administer in cirrhotic patients. The clinical results have been  
105 reported (10). During the intervention period (up to 12 hours post-operatively) the total amount and  
106 type of fluids administered including blood products were recorded prospectively.

107

### 108 *2.5 Organ function assessment*

#### 109 *Cardiac function and systemic haemodynamics*

110 Cardiac function was assessed using haemodynamic measures from the FloTrac™ EV1000  
111 platform. Although the device can track several different haemodynamic measures, the SV and CO

112 were reported on an hourly basis. The mean difference in SV and CO between the two groups were  
113 compared at baseline, six hours (mid-intervention) and 12 hours (end of intervention period). To  
114 understand the effect of GDFT intervention over time on haemodynamic parameters we also  
115 compared the mean change in SV and CO from baseline to 6 and 12 hours between the two groups.

#### 116 *Liver graft function*

117 Liver function tests were recorded for the initial 7 postoperative days. Early allograft dysfunction was  
118 defined by the presence of bilirubin  $\geq 10$  mg/dl; INR  $\geq 1.6$ ; aminotransferase level (alanine  
119 aminotransferase (ALT) or aspartate aminotransferase (AST))  $> 2000$  IU/ml within the first 7  
120 postoperative days (13). The peak and day 3 postoperative transaminase values were also  
121 compared, as independent markers associated with 1-year patient and graft survival (14,15). Graft  
122 function data for 3 months and 1-year follow-up were collected from the National Health Service  
123 Blood and Transplant (NHSBT) database.

#### 124 *Pulmonary function*

125 As an assessment of pulmonary function, time to extubation, arterial blood gas (ABG) (pH, PaCO<sub>2</sub>,  
126 PaO<sub>2</sub>, HCO<sub>3</sub>, base excess (BE)) and ventilator parameters (respiratory rate (RR), tidal volume (TV),  
127 peak end-expiratory pressure (PEEP), peak inspiratory pressure (PIP) and pressure support (PS))  
128 were recorded during the intervention period. To assess acute lung injury, we calculated PaO<sub>2</sub>: FiO<sub>2</sub>  
129 ratios. A ratio of  $< 300$  (mmHg) was defined as acute lung injury (ALI) according to Berlin criteria for  
130 mild acute respiratory distress syndrome (ARDS) (16). Dynamic pulmonary compliance was derived  
131 using a standard formula ( $C_{dyn} = V_T / (PIP - PEEP)$ ). Early inpatient pulmonary complications including  
132 chest infection and pulmonary effusions were captured (see below).

133

#### 134 *Renal function*

135 Serum creatinine was recorded in the first 7 post-operative days as well as 3 months and 1-year  
136 follow up. Acute kidney injury (AKI) was defined using the Kidney Disease Improving Global  
137 Outcomes (KDIGO) score for the first 7 days (17). The highest 7-day KDIGO score for each patient

138 was used for comparison between two groups. At 3 months and 1 year the need for renal  
139 replacement therapy and serum urea and creatinine were used to assess LT related renal  
140 dysfunction.

#### 141 *Complications*

142 The post-operative morbidity score (POMS) was used for assessing complications in pulmonary,  
143 infectious, renal, gastrointestinal, cardiovascular, neurological, wound infections, haematological and  
144 pain (18). These were calculated up to the time of hospital discharge and at 3- and 6-months follow-  
145 up.

146

#### 147 *2.6 Statistical analysis*

148 As a feasibility study, a sample size of 60 patients was chosen to enable estimating the effect size  
149 and subsequent power calculation (19). Prospectively collected data was stored on a secure  
150 electronic REDCap (Research electronic Data Capture) database. Non-parametric data were  
151 presented as medians and interquartile range. Mean and standard deviation was used for parametric  
152 data. Mann-Whitney U test was used for comparison of baseline and outcome measures between  
153 the two groups. Pearson's correlation was used for investigating the relationship between fluid  
154 volume administration and renal function (serum creatinine) and pulmonary function ( $\text{PaO}_2$ :  $\text{FiO}_2$   
155 ratios and  $\text{PaO}_2$ ). Graphs are plotted using medians and inter-quartile range and mean profile plots  
156 with 95% confidence interval where indicated. Statistical analysis was performed using Minitab® 19  
157 Statistical Software and graphs produced using GraphPad Prism 8®.

158

### 159 **3. Results**

160 The results of the COLT trial have been reported according to the CONSORT guidelines (20). Sixty  
161 eligible patients with liver cirrhosis undergoing LT were randomised to GDFT (n=30) or SC (n=30).  
162 All sixty patients completed the intervention period. There was one inpatient death in each group and  
163 one death in the SC group post-hospital discharge. No patients were lost to follow-up during the



164 study (figure 2). The baseline recipient and donor characteristics in both groups are demonstrated in  
165 table 1.

166

### 167 3.1 Intravenous fluid administration

168 The GDFT group received a significantly higher total volume of fluid during the 12-hour intervention  
169 (GDFT 5317 (2335) vs. SC 3807 (1345) ml,  $p=0.003$ ); in particular, crystalloids (GDFT 3968 (2073)  
170 vs. SC 2510 (1027) ml,  $p=0.002$ ). Additional fluid volumes used to dilute intravenous medications  
171 were similar in both groups. There was no difference in the volume of blood products or other  
172 infusions between the two groups (table 2).

173

### 174 3.2 Cardiac function

175 Overall, there was no evidence that the GDFT protocol improved cardiac output when considered  
176 over the entire 12-hour evaluation period. Neither GDFT or SC resulted in an overall increase in SV  
177 readings from baseline to 6 hours or from baseline to 12 hours. The mean SV over time is  
178 demonstrated in figure 3. There were no differences between the two groups in SV at any of these  
179 time points. In the GDFT group, there was a non-significant trend of reduction in SV by 10% over 12  
180 hours (from 100 (34) ml to 91 (31) ml) whilst there was minimal change in the SC group (table 3).  
181 The change in SV ( $\Delta SV$ ) over time was not statistically significant. The CO reduced over time in both  
182 groups between baseline and the 12 hours of intervention (figure 4). There was no statistical  
183 difference in cardiac output between the two groups at baseline, 6 or 12 hours of ICU admission  
184 (table 4). In the GDFT group, there was a marked reduction in CO between baseline and 6 hours of  
185 intervention. The change in CO ( $\Delta CO$ ) was significantly higher in GDFT in the first 6 hours of  
186 intervention compared to SC. However, the  $\Delta CO$  from 6 hours to completion of the intervention at 12  
187 hours was similar in both groups.

188

### 189 3.3 Respiratory function

190 Most patients remained intubated and mechanically ventilated for the duration of the study, as the  
191 mean time to extubation was 12.5 hours post op across both groups. There was no difference  
192 demonstrated in mean time to extubation between the GDFT and SC groups (12.5h (39.5) vs. 12.0h  
193 (33),  $p=0.95$ ). The composite mean profile plots for the arterial blood gas (ABG) measurements for  
194 the first 3 post-operative days are shown in [figure 5](#). Routine ABG analysis was only performed on  
195 25 patients on the third post-operative day. There is a general trend of resolution of acidosis, and  
196 reduction in  $FiO_2$  in both groups at 6 and 12 hours of ICU stay. However, there was no difference  
197 between the two groups at any time-point.

198

### 199 *3.4 Lung injury*

200 The SC group had a trend towards lower  $PaO_2:FiO_2$  ratios at the end of the intervention period but  
201 there was no statistical difference between the two groups at any time point ([figure 6](#)). Similarly, there  
202 was no difference demonstrated in any of the ventilatory measures in the first 24 hours of ICU  
203 admission as shown in [table 5](#). There was no correlation between the total fluid volume administered  
204 and  $PaO_2:FiO_2$  ratios ( $r=-0.09$ ,  $p=0.499$ ) or  $PaO_2$  at 12 hours ( $r=-0.17$ ,  $p=0.234$ ).

205

### 206 *3.5 Renal and liver graft function*

207 Pre-operative liver and renal function tests were similar at baseline ([table 6](#)). There was no difference  
208 demonstrated between the two groups in peak ALT/AST values or post-operative urea and creatinine  
209 values in the first seven days. Serum creatinine was significantly elevated over the first two post-  
210 operative days in both groups (baseline  $77\mu\text{mol/L}$ , day one  $87\mu\text{mol/L}$   $p=0.039$ , day two  $107\mu\text{mol/L}$   
211  $p=0.001$ ) ([figure 7](#)). Renal function improved by day five to baseline levels. There were no differences  
212 in the immediate post-operative (7 days) renal function between the GDFT and SC groups. To  
213 account for outliers and change from baseline, the KDIGO score was calculated for each patient in  
214 the first week post-LT period ([figure 8](#)). There was no significant difference in the highest KDIGO  
215 scores for the first 7 days post liver transplantation (GDFT 0.77 vs. SC 1,  $p=0.405$ ). There was also

216 no correlation between the volume of fluid administered and the post-operative day one KDIGO  
217 scores for AKI ( $r=0.07$ ,  $p=0.573$ ) or day one creatinine ( $r=0.152$ ,  $p=0.253$ ).

218

### 219 3.6 Follow-up

220 At discharge, there were no differences demonstrated between the two groups for any of the POMS  
221 categories (table 7). However, there were significant increases in neurological complications at 90  
222 days in the GDFT group ( $p=0.001$ ) and cardiovascular complications at 6 months in the SC group  
223 ( $p=0.009$ ). These differences were only significant at these specific time-points.

224 All patients were assessed in transplant clinic at 3 months and 1 year. There was no difference in  
225 graft failure or graft function (table 8). There was one death at 3 months in the GDFT vs two in SC  
226 group. Renal impairment and requirement for transient renal filtration rates were similar in both  
227 groups (table 9). Only one patient, in the SC group, required long term renal replacement therapy.

228

229

#### 230 4. Discussion

231 There is no high-quality evidence that GDFT improves the outcome of LT surgery. We therefore  
232 performed a feasibility randomised controlled trial of GDFT vs. SC in the early post-operative period  
233 (first 12 hours) following LT. We demonstrated GDFT to be safe and feasible (10). The COLT  
234 feasibility RCT showed that a GDFT algorithm (SV optimisation) resulted in a significantly higher  
235 volume of crystalloid (5.3 L vs 3.8 L) administration in the immediate 12 hours post LT. Increased  
236 fluid administration immediately post LT has previously been associated with increased respiratory  
237 complications (21,22). In view of the higher fluid administration in the GDFT group we postulated that  
238 this could lead to fluid overload and pulmonary oedema. Despite receiving on average 1.5 L per  
239 patient more intravenous fluids than the SC group, we did not observe a significant rise in the early  
240 pulmonary complications. Both groups had similar time to extubation and the early respiratory  
241 function as assessed by ABG and ventilatory parameters were not adversely affected. An important  
242 observation in this study is the correction of blood gas parameters over the first 12 hours in both  
243 groups suggesting this is the key period for correcting physiology following liver transplant. It is also  
244 important to note that although there was no statistical difference in PaO<sub>2</sub>:FiO<sub>2</sub> ratios, only rarely did  
245 patients cross the threshold for acute lung injury over the first 3 days post-OLT.

246 Increased crystalloid infusion and a positive fluid balance have also been reported in observational  
247 studies to be a risk factors for renal dysfunction post-OLT (9,21). We did not observe a significant  
248 difference in the early renal function and KDIGO scores for AKI between the two groups. Given that  
249 renal impairment in both groups was most apparent after the second post operative day it may be  
250 that renal perfusion and fluid therapy has less impact on renal function post liver transplantation than  
251 circulating inflammatory mediators and the commencement of nephrotoxic immunosuppression (23).  
252 There were also no differences demonstrated in allograft dysfunction or the need for renal  
253 replacement therapy at any point through to one year follow up.

254 The failure to detect a difference in the early pulmonary and renal function is likely to be secondary  
255 to the study size and the presence of a type one statistical error as previous studies demonstrating  
256 changes in clinical outcome with cardiac-output guided fluid therapy as an intervention in patients

257 undergoing elective major general surgery have included over 700 patients (24,25). Fluid therapy is  
258 considered a 'complex intervention' (26) especially in the setting of LT. Therefore, the possibility  
259 remains that the volume replacement algorithm is suitable and relevant for patients undergoing major  
260 general and cardiac surgery but not those with longstanding liver cirrhosis. SV optimisation was the  
261 key intervention, but there were no differences observed in the SV and CO when viewed over the  
262 entire period of the intervention. This is contrary to studies demonstrating clinical benefit with  
263 improvement in haemodynamic parameters in patients undergoing high risk general surgical  
264 operations (27). We observed a reduction in CO over time as has been shown in previous studies  
265 (28). The initially higher CO readings may be secondary to the surgical stress and liver cirrhosis and  
266 normalising over time with the implantation of a non-cirrhotic liver. Hence, failure to observe a  
267 difference in haemodynamic parameters in the COLT trial poses important questions: a)  
268 appropriateness of the GDFT protocol using SV optimisation in advanced liver cirrhosis and whether  
269 crystalloids are the optimal fluid of choice to increase the SV b) the device accuracy used to monitor  
270 response to the intervention.

271 Although there is no consensus on the appropriate 'goal' for perioperative GDFT, several post-  
272 operative GDFT trials which have shown a reduction in complications after major abdominal surgery  
273 have used SV-optimisation protocol extrapolated from the Frank-Starling curve (24,25,27). 'Fluid  
274 responsiveness' in this respect is defined as a rise in SV by >10% to a pre-load expansion via a fluid  
275 bolus which suggests recruitable SV on the Frank-Starling curve until no further rise is observed (29).  
276 This functional definition of euvoemia has been used in GDFT protocols to avoid the harmful effects  
277 of hypoperfusion of end-organs or fluid overload and oedema leading to complications. However,  
278 predicting fluid responsiveness is complex and influenced by several peri-operative factors which  
279 may alter the Frank-Starling relationship such as surgical stress, central blood volume, orthostatic  
280 changes and mechanical ventilation and the use of vasopressors (30). This is further compounded  
281 by factors specific to this cohort of patients, which is the effect of cirrhotic cardiomyopathy, autonomic  
282 dysfunction secondary to chronic alcohol abuse and major haemodynamic changes seen in liver  
283 cirrhosis. Whether this functional definition of euvoemia applies to patients with severely altered

284 haemodynamics and a degree of cardiac dysfunction due to liver cirrhosis is not known and requires  
285 in depth study of the Frank Starling relationship to devise appropriate haemodynamic derived GDFT  
286 methods in cirrhotic patients. Most patients proceeding to LT have advanced liver cirrhosis (Child B  
287 or C). A recent study which may support our findings suggests that although a fluid challenge did  
288 result in a significant rise in SV in mild liver cirrhosis (Child A), this was not the case for advanced  
289 liver cirrhosis (Child B or C) post liver transplantation (31). Furthermore, this was achieved using a  
290 colloid (albumin 5%) rather than a crystalloid. This phenomenon could be due to altered physiological  
291 fluid handling in advanced liver cirrhosis (4).

292 GDFT is based on improving cardiac function but in those with associated heart disease, such as  
293 cirrhotic cardiomyopathy, this may not be possible. Cardiac dysfunction in liver cirrhosis may only  
294 become apparent under stressful conditions as reduced ventricular contractility is masked by  
295 significant arterial vasodilation and increased arterial compliance (32). Lastly, the FloTrac / Vigileo™  
296 (Edwards Lifesciences, Irvine, CA) was used in this trial as a non-invasive self-calibrating pulse  
297 contour analysis device which estimates CO readings based on a predefined algorithm. Despite the  
298 software updates to improve accuracy on this device, it still has a high error rate of more than 50%  
299 in estimating haemodynamic variables in the low resistance states observed in cirrhotic patients post  
300 OLT which is below the current benchmarks (33–35).

301 The optimal GDFT protocol for peri-operative management of LT patients has not been defined and  
302 a major hurdle is the assessment of cardiac preload given the major haemodynamic changes in  
303 cirrhosis. Future design of GDFT protocols in patients with advanced cirrhosis should consider the  
304 complexities relating specifically to patients with advanced liver cirrhosis.

305

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314

## 315 **6. Ethics and Registration**

316 The study was approved by University College London Bloomsbury Research Ethics Committee  
317 (Ref: 180463) and registered at ISRCTN (10329248) (36) and Research Registry (UIN  
318 researchregistry7434) (37).

319

## 320 **7. Provenance and peer review**

321 This work is not commissioned and is externally peer-reviewed.

322

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459 **Table 1. Recipient and donor baseline characteristics**

|  |                           | GDFT arm (n=30)  | SC arm (n=30)    |
|--|---------------------------|------------------|------------------|
| <b>Recipients</b>                                  |                           |                  |                  |
| Age (years)  |                           | 53 (30 – 79)     | 58 (31 – 68)     |
| Gender   | Male                      | 20 (67%)         | 23 (77%)         |
|  | Female                    | 10 (33%)         | 7 (23%)          |
| MELD score   |                           | 14 (7 – 28)      | 14 (7 – 27)      |
| UKELD score  |                           | 54 (47 – 66)     | 54 (47 – 67)     |
| Reason for transplantation                         | Alcohol cirrhosis         | 11 (30%)         | 12 (32%)         |
|  | Hepatitis C               | 3 (8%)           | 9 (24%)          |
|  | Hepatitis B               | 4 (11%)          | 2 (5%)           |
|  | Autoimmune hepatitis      | 2 (5%)           | 1 (3%)           |
|  | Primary biliary cirrhosis | 6 (16%)          | 4 (11%)          |
|  | PSC                       | 2 (5%)           | 0 (0%)           |
|  | Other                     | 9 (24%)          | 10 (26%)         |
| <b>Donor details</b>                               |                           |                  |                  |
| Age (years)  |                           | 51 (17 – 75)     | 45 (15 – 76)     |
| BMI (kg/m <sup>2</sup> )                           |                           | 25.1 (18.2 – 35) | 24.9 (15.9 – 34) |
| Cause of death                                     | Cerebrovascular accident  | 21 (70%)         | 15 (50%)         |
|  | Hypoxic brain damage      | 6 (20%)          | 6 (20%)          |
|  | Other <sup>1</sup>        | 3 (10%)          | 9 (30%)          |
| Donor type   | DBD                       | 24 (80%)         | 25 (83%)         |
|  | DCD                       | 6 (20%)          | 5 (17%)          |
| Donor liver capsular damage                        |                           | 2 (7%)           | 4 (13%)          |
| Donor liver steatosis                              | None                      | 15 (52%)         | 21 (70%)         |
|  | Mild                      | 8 (27%)          | 7 (23%)          |
|  | Moderate                  | 6 (21%)          | 2 (7%)           |
| Donor liver appearance                             | Healthy                   | 19 (70%)         | 22 (76%)         |
|  | Suboptimal                | 8 (30%)          | 7 (24%)          |
| Graft type   | Spilt liver               | 4 (13%)          | 3 (10%)          |
|  | Whole liver               | 26 (87%)         | 27 (90%)         |
| OLT type   | Conventional              | 10 (33%)         | 14 (47%)         |
|  | Piggyback                 | 20 (67%)         | 16 (53%)         |
| Cold ischaemic time (hours)                        |                           | 9.6 (0.5 – 16.3) | 9.3 (3.5 – 19)   |
| Initial warm ischaemic time (hours) <sup>2</sup>   |                           | 0.7 (0.3 – 1.8)  | 0.6 (0.3 – 2.6)  |
| Secondary warm ischaemic time (hours) <sup>3</sup> |                           | 0.8 (0.3 – 2.2)  | 0.7 (0.2 – 1.5)  |

Data expressed as medians (range or % frequency)

GDFT = Goal Directed Fluid Therapy, SC = Standard Care, BMI = Body Mass Index, UKELD = United Kingdom Model for End-Stage Liver Disease score, MELD = Model for End-Stage Liver Disease score, OLT = Orthotopic Liver Transplantation

<sup>1</sup> 'Other' includes brain tumour, trauma, poisoning, cardiac arrest

<sup>2</sup> Time from circulatory arrest to liver on ice

<sup>3</sup> Time to liver revascularisation

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462 **Table 2. Intravenous fluid and blood product volumes**

|                                  | <b>GDFT arm (n=30)</b> | <b>SC arm (n=30)</b> | <b>p-value</b> |
|----------------------------------|------------------------|----------------------|----------------|
| <b>Crystalloids (mL)</b>         | <b>3968 (2073)</b>     | <b>2510 (1027)</b>   | <b>0.002*</b>  |
| Additional fluid volume* (mL)    | 864 (609)              | 779 (473)            | 0.684          |
| <b>Total IV fluid input (mL)</b> | <b>5317 (2335)</b>     | <b>3807 (1345)</b>   | <b>0.003*</b>  |
| <b>Additional blood products</b> |                        |                      |                |
| 20% Human Albumin Solution (mL)  | 93 (295)               | 74 (209)             | 0.960          |
| Packed red blood cells (mL)      | 177 (456)              | 150 (316)            | 0.646          |
| Fresh frozen plasma (mL)         | 81 (234)               | 145 (323)            | 0.425          |
| Platelets (mL)                   | 62 (175)               | 76 (165)             | 0.539          |
| Cryoprecipitate (mL)             | 72 (394)               | 73 (156.64)          | 0.056          |

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465 **Table 3. Stroke Volume (ml)**

|                 | <b>GDFT arm (n=30)</b> | <b>SC arm (n=30)</b> | <b>Mean difference (95% CI)</b> | <b>p-value</b> |
|-----------------|------------------------|----------------------|---------------------------------|----------------|
| <b>Baseline</b> | 99.9 (34.3)            | 89.77 (26.6)         | 10.1 (-5.9 – 26.1)              | 0.211          |
| <b>6 hours</b>  | 90.4 (29.8)            | 92.4 (29.0)          | -1.99 (-17.3 – 13.4)            | 0.796          |
| <b>12 hours</b> | 90.5 (31.4)            | 88.6 (25.0)          | 1.93 (-12.7 – 16.6)             | 0.793          |

Stroke volume data is presented as mean (SD)

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468 **Table 4. Cardiac output (L/min)**

|                 | <b>GDFT arm (n=30)</b> | <b>SC arm (n=30)</b> | <b>Mean difference (95% CI)</b> | <b>p-value</b> |
|-----------------|------------------------|----------------------|---------------------------------|----------------|
| <b>Baseline</b> | 8.94 (3.59)            | 7.95 (1.74)          | 0.99 (-0.47 – 2.45)             | 0.182          |
| <b>6 hours</b>  | 7.09 (1.84)            | 7.48 (2.16)          | -0.39 (-1.44 – 0.66)            | 0.458          |
| <b>12 hours</b> | 6.90 (1.78)            | 7.22 (1.98)          | -0.32 (-1.30 – 0.65)            | 0.509          |

Cardiac output data is presented as mean (SD)

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471 **Table 5. Ventilatory parameters**

|  | <b>Time point</b> | <b>GDFT arm (n=30)</b> | <b>SC arm (n=30)</b> | <b>p-value</b> |
|--|-------------------|------------------------|----------------------|----------------|
| <b>Respiratory rate (bpm)</b>                      | ICU admission     | 14 (3.5)               | 14 (4)               | 0.586          |
|  | 6 hours           | 14 (5)                 | 14(4)                | 0.864          |
|  | 12 hours          | 14 (3.8)               | 13.5 (4.8)           | 0.781          |
|  | Day 2             | 12 (6)                 | 12 (4)               | 0.421          |
| <b>Tidal Volume (mL)</b>                           | ICU admission     | 566 (121)              | 601 (115)            | 0.166          |
|  | 6 hours           | 581 (162)              | 584 (172.5)          | 0.609          |
|  | 12 hours          | 587 (170)              | 635 (345.8)          | 0.603          |
|  | Day 2             | 548 (73)               | 550 (165.3)          | 0.943          |
| <b>PEEP (cmH<sub>2</sub>O)</b>                     | ICU admission     | 6.1(1.7)               | 5.8 (1.25)           | 0.518          |
|  | 6 hours           | 6.3 (2.9)              | 6 (0.8)              | 0.644          |
|  | 12 hours          | 5.9 (4.1)              | 6.1 (0.9)            | 0.533          |
|  | Day 2             | 6.3 (4)                | 7.3 (3.6)            | 1.000          |
| <b>PIP (cmH<sub>2</sub>O)</b>                      | ICU admission     | 21 (5)                 | 20 (6)               | 0.076          |
|  | 6 hours           | 21 (10.5)              | 21 (5)               | 0.791          |
|  | 12 hours          | 20.5 (9)               | 19.5 (7)             | 0.504          |
|  | Day 2             | 25 (4)                 | 19 (9.25)            | 0.221          |
| <b>Pressure Support (cmH<sub>2</sub>O)</b>         | ICU admission     | 12 (10)                | 12 (7)               | 0.079          |
|  | 6 hours           | 12 (10.5)              | 11 (7.5)             | 0.204          |
|  | 12 hours          | 12 (9)                 | 12 (7)               | 0.721          |
|  | Day 2             | 12 (5)                 | 12.5 (5.5)           | 0.828          |
| <b>Pulmonary Compliance* (ml/cmH<sub>2</sub>O)</b> | ICU admission     | 39.1 (17.3)            | 45.2 (27.8)          | 0.137          |
|  | 6 hours           | 45.8 (27.6)            | 39.5 (14.6)          | 0.987          |
|  | 12 hours          | 40.7 (37.6)            | 49.1 (54.2)          | 0.493          |
|  | Day 2             | 31 (14.6)              | 45.2 (17.8)          | 0.175          |

Data expressed as median (IQR), PEEP = Positive End Expiratory pressure, PIP = Peak Inspiratory Pressure

\* Pulmonary Compliance calculated by 'Tidal Volume/(PIP-PEEP)'

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474 **Table 6. Liver and renal function**

|   | <b>GDFT arm (n=30)</b> | <b>SC arm (n=30)</b> | <b>p- value</b> |
|---|------------------------|----------------------|-----------------|
| <b>Pre-operative liver function</b>       |                        |                      |                 |
| Prothrombin time (s)                      | 14.2 (11.3 – 22.5)     | 13.5 (12 – 17.6)     | 0.896           |
| INR                                       | 1.3 (1 – 2)            | 1.2 (1 – 1.6)        | 0.663           |
| APTT (s)                                  | 37.4 (31.9 – 59.3)     | 39.3 (33.1 – 59.8)   | 0.768           |
| Fibrinogen                                | 2.6 (1.4 – 3.7)        | 2.2 (1.5 – 3.5)      | 0.790           |
| Bilirubin                                 | 47.5 (6 – 241)         | 45.5 (10 – 241)      | 0.895           |
| ALT                                       | 51.5 (19 – 131)        | 46.5 (22 – 129)      | 0.322           |
| AST                                       | 68 (28 – 148)          | 37 (13 – 72)         | 0.121           |
| ALP                                       | 143.5 (69 – 455)       | 108 (46 – 838)       | 0.767           |
| Albumin                                   | 31 (21 – 42)           | 38.5 (27 – 47)       | 0.084           |
| <b>Pre-operative renal function</b>       |                        |                      |                 |
| Serum creatinine                          | 73 (46 – 111)          | 71.5 (56 – 121)      | 0.921           |
| Urea                                      | 7.6 (2.4 – 12.9)       | 6.4 (3.3 – 14.2)     | 0.424           |
| Estimated GFR                             | >90 (61 – 90+)         | >90 (54 – 90+)       | 0.640           |
| <b>Peak post-operative liver function</b> |                        |                      |                 |
| Prothrombin time                          | 19.5 (13.4 – 43)       | 19.9 (11.6 – 33.6)   | 0.905           |
| INR                                       | 1.75 (1.2 – 4)         | 1.8 (1.1 – 3.3)      | 0.970           |
| APTT                                      | 56.8 (37.1 – 200)      | 70.3 (26.2 – 389)    | 0.132           |
| Fibrinogen                                | 2.5 (1.2 – 11.1)       | 2.4 (0.8 – 4.8)      | 0.939           |
| Bilirubin                                 | 102.5 (57 – 355)       | 79 (16 – 239)        | 0.067           |
| ALT                                       | 727 (179 – 3967)       | 730.5 (207 – 6825)   | 0.751           |
| AST                                       | 900.5 (254 – 11286)    | 1050 (106 – 7033)    | 0.595           |
| ALP                                       | 252 (94 – 690)         | 218.5 (89 – 1805)    | 0.739           |
| Albumin                                   | 35 (22 – 48)           | 33.5 (25 – 42)       | 0.347           |
| <b>Peak post-operative renal function</b> |                        |                      |                 |
| Serum creatinine                          | 120 (60 – 364)         | 137 (54 – 428)       | 0.682           |
| Urea                                      | 16.1 (5.3 – 26)        | 14.3 (4.1 – 26.3)    | 0.862           |
| Estimated GFR                             | >90 (41 – 90+)         | >90 (50 – 90+)       | 0.754           |

Data is presented as median (range).

The peak value in the first seven days was selected for individual patients and the median of these taken from across the treatment arm.

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477 **Table 7. Post-operative morbidity score (POMS) for complications**  
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|                  | POMS category      | GDFT arm<br>(n=30) | SC arm (n=30) | p-value |
|------------------|--------------------|--------------------|---------------|---------|
| <b>Discharge</b> | Pulmonary          | 19 (63.33)         | 14 (46.67)    | 0.194   |
|                  | Infectious         | 14 (46.67)         | 11 (36.67)    | 0.432   |
|                  | Renal              | 16 (53.33)         | 16 (53.33)    | 1.000   |
|                  | Gastrointestinal   | 19 (63.33)         | 19 (63.33)    | 1.000   |
|                  | Cardiovascular     | 12 (40)            | 12 (40)       | 1.000   |
|                  | Neurological       | 8 (26.67)          | 10 (33.33)    | 0.573   |
|                  | Wound complication | 2 (6.67)           | 2 (6.67)      | 0.694   |
|                  | Haematological     | 16 (53.33)         | 17 (56.67)    | 0.795   |
|                  | Pain               | 13 (43.33)         | 15 (50)       | 0.605   |
| <b>90 days</b>   | Pulmonary          | 1 (3.57)           | 4 (14.29)     | 0.626   |
|                  | Infectious         | 5 (17.86)          | 15 (53.57)    | 0.898   |
|                  | Renal              | 5 (17.86)          | 7 (25)        | 0.937   |
|                  | Gastrointestinal   | 14 (50)            | 12 (42.86)    | 0.906   |
|                  | Cardiovascular     | 1 (3.57)           | 5 (17.86)     | 0.524   |
|                  | Neurological       | 5 (17.86)          | 1 (3.57)      | 0.001   |
|                  | Wound complication | 1 (3.57)           | 7 (25)        | 0.808   |
|                  | Haematological     | 4 (14.29)          | 5 (17.86)     | 0.686   |
|                  | Pain               | 6 (21.43)          | 6 (21.43)     | 0.203   |
| <b>6 months</b>  | Pulmonary          | 1 (3.57)           | 3 (11.54)     | 0.277   |
|                  | Infectious         | 5 (17.86)          | 7 (26.92)     | 0.423   |
|                  | Renal              | 5 (17.86)          | 7 (26.92)     | 0.423   |
|                  | Gastrointestinal   | 14 (50)            | 11 (42.31)    | 0.571   |
|                  | Cardiovascular     | 1 (3.57)           | 8 (30.77)     | 0.009   |
|                  | Neurological       | 5 (17.86)          | 3 (11.54)     | 0.396   |
|                  | Wound complication | 1 (3.57)           | 0 (0)         | 0.519   |
|                  | Haematological     | 4 (14.29)          | 5 (19.23)     | 0.451   |
|                  | Pain               | 6 (21.43)          | 2 (7.69)      | 0.150   |

Data presented as absolute values in each arm (% frequency) of patients with at least one complication by POMS category.

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481 **Table 8. Liver graft function and survival at 3 months and 1 year**

|  |           | <b>GDFT arm (n=30)</b> | <b>SC arm (n=30)</b> | <b>p – value</b> |
|--|-----------|------------------------|----------------------|------------------|
| <b>Re-transplantation</b>                |           | 1 (3%)                 | 1 (3%)               | NS               |
| <b>Graft failure</b>                     | 3months   | 2 (7%)                 | 3 (10%)              | NS               |
|  | 1year     | 0 (0%)                 | 0 (0%)               | NS               |
| <b>Patient death</b>                     | 3months   | 1 (3%)                 | 2 (7%)               | NS               |
|  | 1year     | 0 (0%)                 | 0 (0%)               | NS               |
| <b>Liver function at 1year follow-up</b> | Bilirubin | 10 (4 – 54)            | 10 (2 – 31)          | 0.858            |
|  | ALT       | 27 (5 – 540)           | 27 (12 – 195)        | 0.845            |
|  | AST       | 25.5 (9 – 340)         | 22.5 (14 – 138)      | 0.379            |
|  | ALP       | 103.5 (36 – 2086)      | 83 (39 – 596)        | 0.209            |

Data is presented as median (range) or absolute number (% frequency)

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484

485 **Table 9. Renal function at 3 months and 1 year**

|                                    |   | <b>GDFT arm<br/>(n=30)</b> | <b>SC arm<br/>(n=30)</b> | <b>p-<br/>value</b> |
|------------------------------------|---|----------------------------|--------------------------|---------------------|
| <b>Renal status at<br/>3months</b> | No/minor renal impairment               | 20 (67%)                   | 22 (73%)                 | NS                  |
|                                    | Required transient renal<br>filtration  | 7 (23%)                    | 7 (23%)                  | NS                  |
|                                    | Required long-term dialysis             | 0 (0%)                     | 1 (3%)                   | NS                  |
| <b>Renal function at<br/>1year</b> | Urea                                    | 8 (4.9 – 13.1)             | 7.25 (5.2 –<br>13.5)     | 0.659               |
|                                    | Serum Creatinine                        | 96 (37 – 146)              | 107.5 (67 –<br>202)      | 0.431               |
|                                    | Transplant related renal<br>dysfunction | 13 (43%)                   | 12 (40%)                 | NS                  |

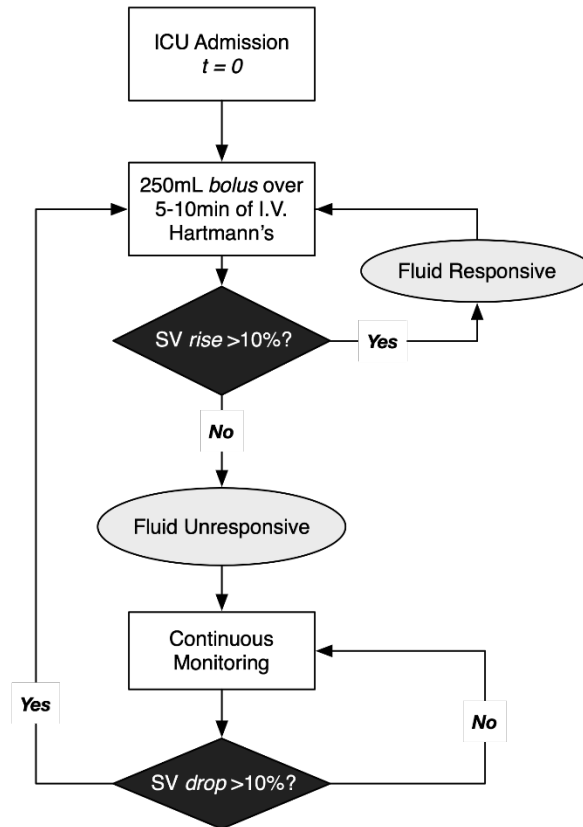
Data is presented as median (range) or absolute number (% frequency)

486

487

488 **Figure 1. GDFT protocol for SV optimisation**

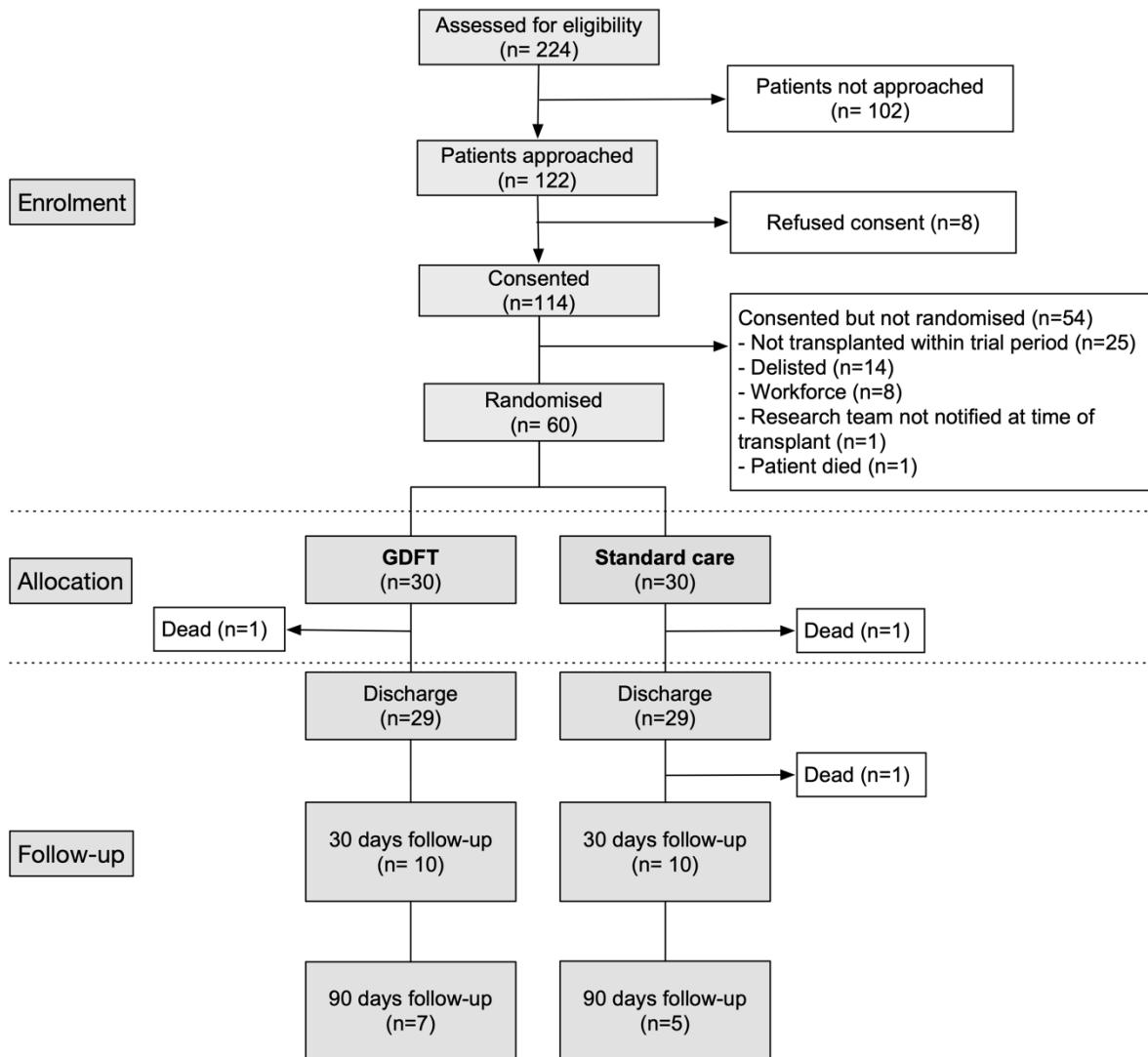
489 An initial bolus infusion of 250mL Hartmann's was given on arrival to ICU; if there was an increase  
490 of >10% in SV the patient was deemed to be fluid responsive and a further bolus was given until no  
491 SV rise was observed to achieve a state of euvoemia (<10% rise in SV after a 250mL bolus of  
492 crystalloid). No maintenance fluids were administered.



493

494

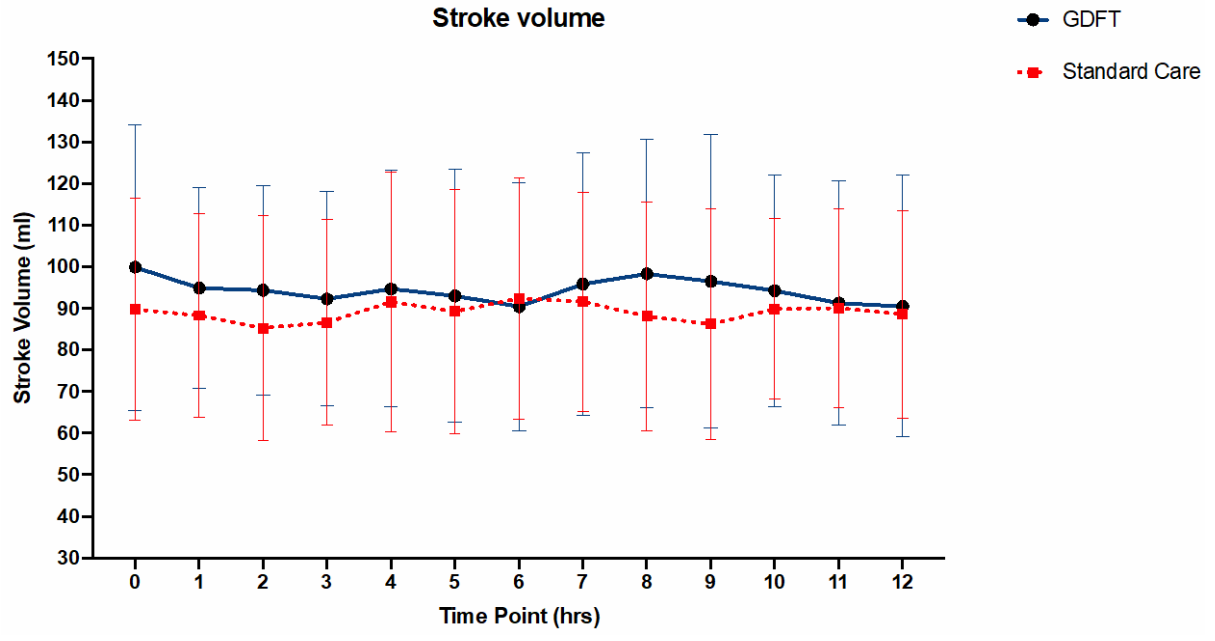
495 **Figure 2. Study CONSORT flow diagram**



496

497

498 **Figure 3. Stroke Volume**



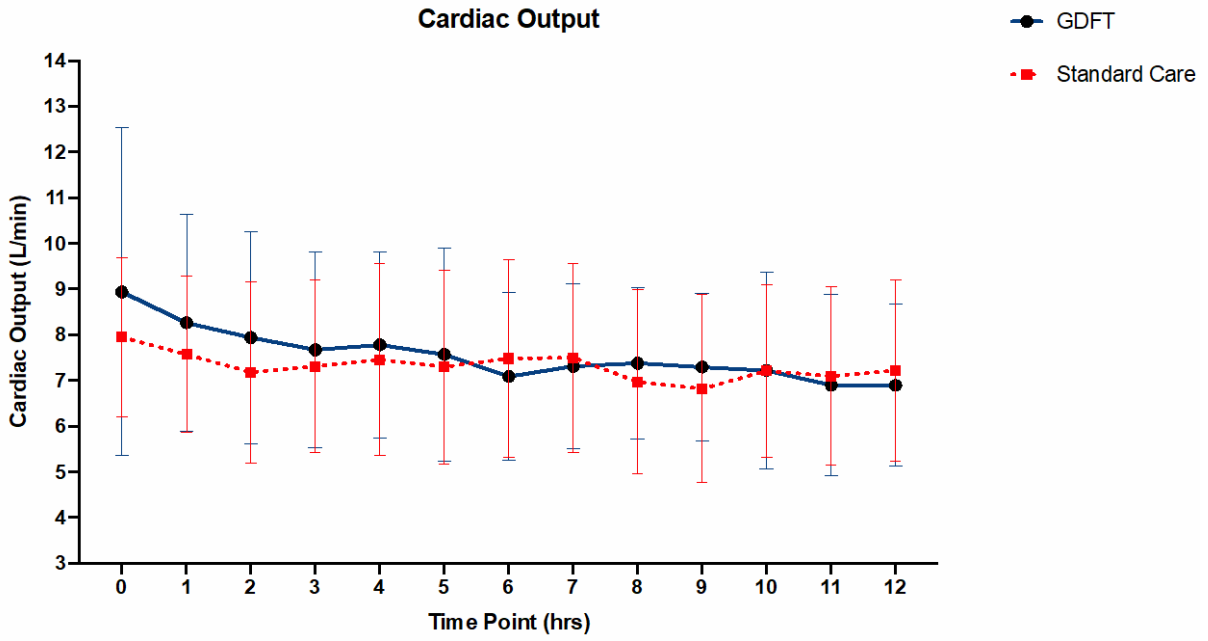
499

500 Mean profile plot with 95% CI

501



502 **Figure 4. Cardiac Output**

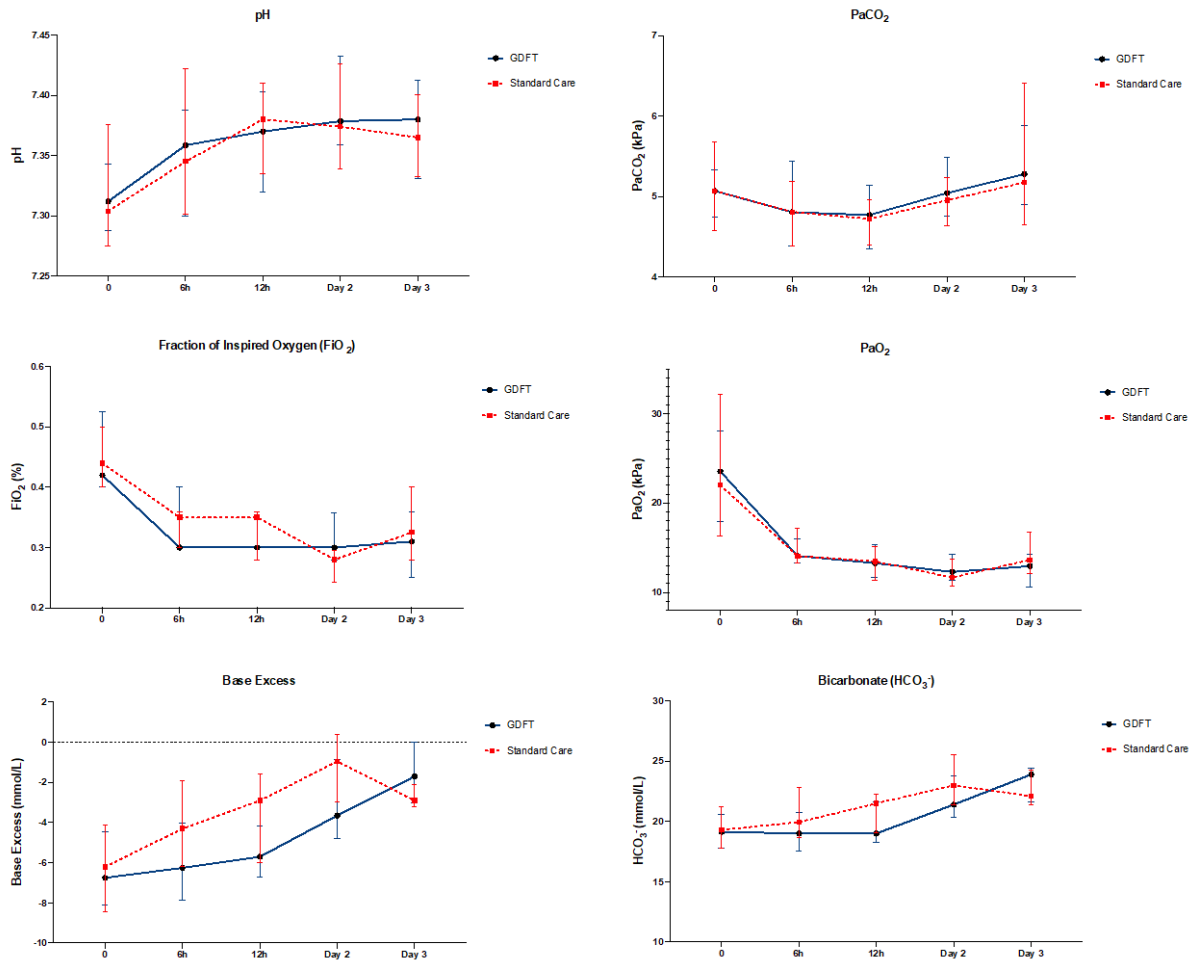


503

504 Mean profile plot with 95% CI

505

506 **Figure 5. Arterial Blood Gas (ABG) parameters**



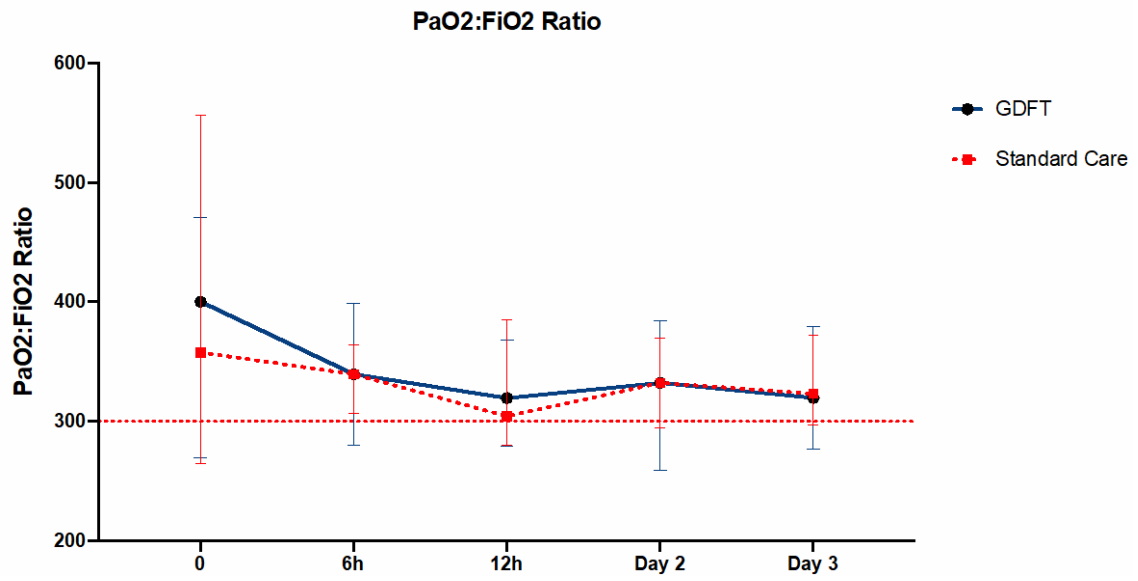
507

508 Mean profile plots with 95% CI

509

510

511 **Figure 6. PaO<sub>2</sub>:FiO<sub>2</sub> ratios**



512

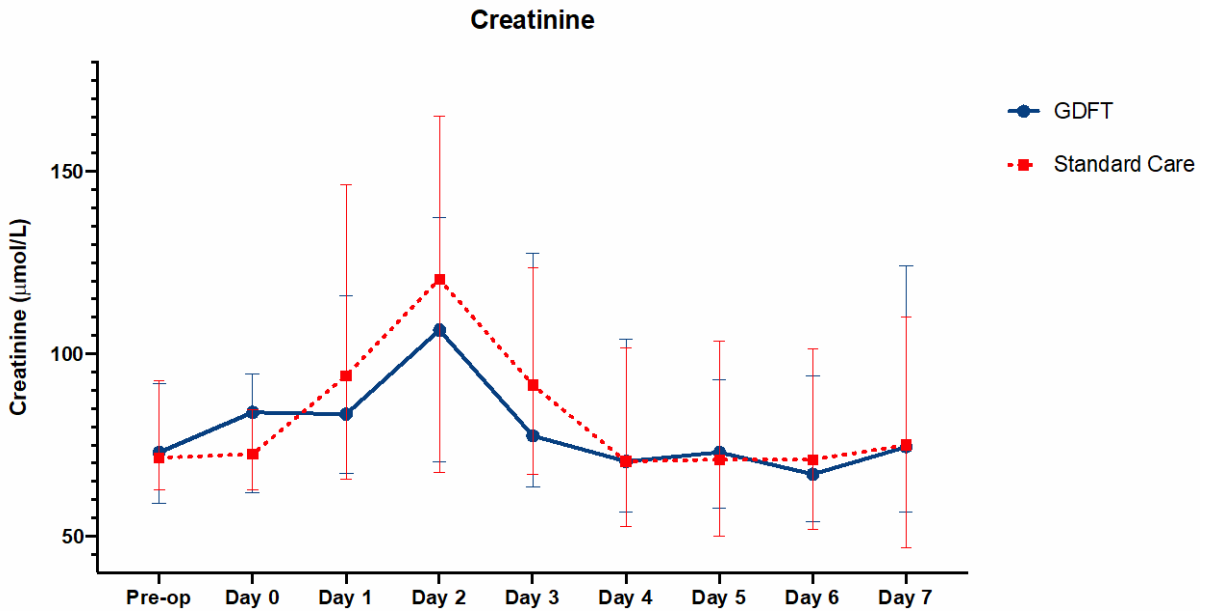
513 PaO<sub>2</sub>:FiO<sub>2</sub> < 300 is consistent with ALI (acute lung injury) or mild ARDS.

514

515

516 **Figure 7. Serum Creatinine**

517



518

519 Mean profile plot with 95% CI

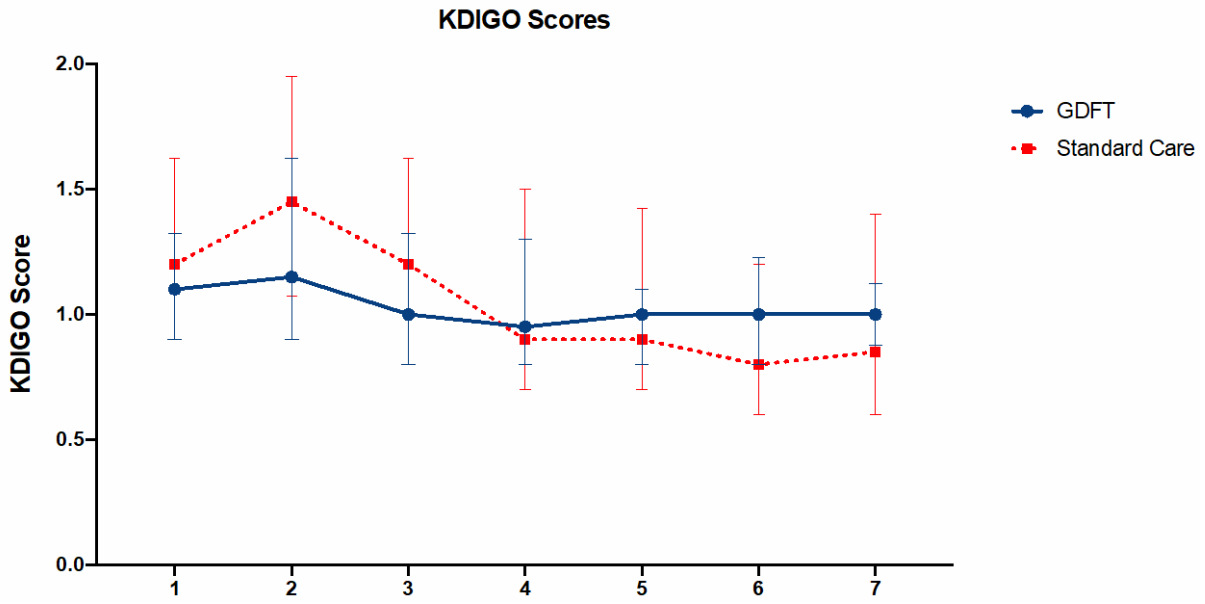
520

521

522

523 **Figure 8. KDIGO scores**

524



525

526 Mean profile plot with 95% CI

527