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

Abstract

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

Methods: Adult patients with liver cirrhosis undergoing liver transplantation were randomised to GDFT or SC for the first 12 hours following surgery as detailed in a published trial protocol. GDFT protocol was based on stroke-volume (SV) optimisation using 250ml crystalloid boluses. Total fluid administration and time to extubation were recorded. Hourly SV and cardiac output (CO) readings were recorded from the non-invasive cardiac output monitoring (NICOM) device in both groups. Pulmonary function was assessed by arterial blood gas (ABG) and ventilatory parameters. Lung injury was assessed using PaO_2:FiO_2 ratios and calculated pulmonary compliance. The KDIGO score was used for determining acute kidney injury. Renal and liver graft function were assessed during the post-operative period and at 3 months and 1-year.

Results: 60 patients were randomised to GDFT (n=30) or SC (n=30). All patients completed the 12h intervention period. GDFT group received a significantly higher total volume of fluid during the 12h trial intervention period (GDFT 5317 (2335) vs. SC 3807 (1345) ml, p=0.003); in particular crystalloids (GDFT 3968 (2073) vs. SC 2510 (1027) ml, p=0.002). There was no evidence of significant difference between the groups in SV or CO during the assessment periods. Time to extubation, PaO2: F_IO_2

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

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

1. Introduction

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

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

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

to the method of assessment of fluid responsiveness and fluid resuscitation end-goals for achieving a euvolemic state as well as the type of fluid administered with or without pharmacological adjuncts.

The COLT trial has demonstrated that it is feasible and safe to randomise patients post liver transplant to GDFT vs. SC using a simple stroke volume (SV) optimisation protocol (10). This trial was not powered to address efficacy. The study provided an opportunity to evaluate organ end-organ function in cirrhotic patients randomly allocated to GDFT or SC for the first 12 hours following LT. The aim of this study is to report the effect of post-operative GDFT on post-operative end-organ function in patients with liver cirrhosis undergoing LT.

2. Patients and Methods

2.1 Study setting and patients

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

2.2 Study design and randomisation

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

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

2.3 Intervention and blinding

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

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

2.4 Clinical outcome measures

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

2.5 Organ function assessment

Cardiac function and systemic haemodynamics

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

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

Liver graft function

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

Pulmonary function

As an assessment of pulmonary function, time to extubation, arterial blood gas (ABG) (pH, $PaCO_2$, PaO_2, HCO_3, base excess (BE)) and ventilator parameters (respiratory rate (RR), tidal volume (TV), peak end-expiratory pressure (PEEP), peak inspiratory pressure (PIP) and pressure support (PS)) were recorded during the intervention period. To assess acute lung injury, we calculated PaO_2: FIO_2 ratios. A ratio of <300 (mmHg) was defined as acute lung injury (ALI) according to Berlin criteria for mild acute respiratory distress syndrome (ARDS) (16). Dynamic pulmonary compliance was derived using a standard formula ($C_{dyn} = V_T / (PIP – PEEP)$. Early inpatient pulmonary complications including chest infection and pulmonary effusions were captured (see below).

Renal function

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

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

Complications

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

2.6 Statistical analysis

As a feasibility study, a sample size of 60 patients was chosen to enable estimating the effect size and subsequent power calculation (19). Prospectively collected data was stored on a secure electronic REDCap (Research electronic Data Capture) database. Non-parametric data were presented as medians and interquartile range. Mean and standard deviation was used for parametric data. Mann-Whitney U test was used for comparison of baseline and outcome measures between the two groups. Pearson's correlation was used for investigating the relationship between fluid volume administration and renal function (serum creatinine) and pulmonary function (PaO_2: FIO_2 ratios and PaO_2). Graphs are plotted using medians and inter-quartile range and mean profile plots with 95% confidence interval where indicated. Statistical analysis was performed using Minitab® 19 Statistical Software and graphs produced using GraphPad Prism 8©.

3. Results

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

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

3.1 Intravenous fluid administration

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

3.2 Cardiac function

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

3.3 Respiratory function

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

3.4 Lung injury

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

3.5 Renal and liver graft function

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

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

3.6 Follow-up

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

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

4. Discussion

There is no high-quality evidence that GDFT improves the outcome of LT surgery. We therefore performed a feasibility randomised controlled trial of GDFT vs. SC in the early post-operative period (first 12 hours) following LT. We demonstrated GDFT to be safe and feasible (10). The COLT feasibility RCT showed that a GDFT algorithm (SV optimisation) resulted in a significantly higher volume of crystalloid (5.3 L vs 3.8 L) administration in the immediate 12 hours post LT. Increased fluid administration immediately post LT has previously been associated with increased respiratory complications (21,22). In view of the higher fluid administration in the GDFT group we postulated that this could lead to fluid overload and pulmonary oedema. Despite receiving on average 1.5 L per patient more intravenous fluids than the SC group, we did not observe a significant rise in the early pulmonary complications. Both groups had similar time to extubation and the early respiratory function as assessed by ABG and ventilatory parameters were not adversely affected. An important observation in this study is the correction of blood gas parameters over the first 12 hours in both groups suggesting this is the key period for correcting physiology following liver transplant. It is also important to note that although there was no statistical difference in PaO_2:FiO_2 ratios, only rarely did patients cross the threshold for acute lung injury over the first 3 days post-OLT.

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

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

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

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

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

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

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

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6. Ethics and Registration

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

7. Provenance and peer review

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

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

		GDFT arm (n=30)	SC arm (n=30)
Recipients			
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%)
Donor details			
Age (years)		51 (17 – 75)	45 (15 – 76)
BMI (kg/m^2)		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[1]	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)[2]		0.7 (0.3 – 1.8)	0.6 (0.3 – 2.6)
Secondary warm ischaemic time (hours)[3]		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 Kingdome Model for End-Stage Liver Disease score, MELD = Model for End-Stage Liver Disease score, OLT = Orthotopic Liver Transplantation

[1] 'Other' includes brain tumour, trauma, poisoning, cardiac arrest

[2] Time from circulatory arrest to liver on ice

[3] Time to liver revascularisation

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

	GDFT arm (n=30)	SC arm (n=30)	p-value
Crystalloids (mL)	**3968 (2073)**	**2510 (1027)**	**0.002***
Additional fluid volume* (mL)	864 (609)	779 (473)	0.684
Total IV fluid input (mL)	**5317 (2335)**	**3807 (1345)**	**0.003***
Additional blood products			
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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Table 3. Stroke Volume (ml)

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

Stroke volume data is presented as mean (SD)

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

	GDFT arm (n=30)	SC arm (n=30)	Mean difference (95% CI)	p-value
Baseline	8.94 (3.59)	7.95 (1.74)	0.99 (-0.47 – 2.45)	0.182
6 hours	7.09 (1.84)	7.48 (2.16)	-0.39 (-1.44 – 0.66)	0.458
12 hours	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**

	Time point	GDFT arm (n=30)	SC arm (n=30)	p-value
Respiratory rate (bpm)	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
Tidal Volume (mL)	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
PEEP (cmH_2O)	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
PIP (cmH_2O)	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
Pressure Support (cmH_2O)	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
Pulmonary Compliance* (ml/cmH_2O)	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**

	GDFT arm (n=30)	SC arm (n=30)	p– value
Pre-operative liver function			
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
Pre-operative renal function			
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
Peak post-operative liver function			
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
Peak post-operative renal function			
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 (n=30)	SC arm (n=30)	p-value
Discharge	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
90 days	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
6 months	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**

		GDFT arm (n=30)	SC arm (n=30)	p – value
Re-transplantation		1 (3%)	1 (3%)	NS
Graft failure	3months	2 (7%)	3 (10%)	NS
	1year	0 (0%)	0 (0%)	NS
Patient death	3months	1 (3%)	2 (7%)	NS
	1year	0 (0%)	0 (0%)	NS
Liver function at 1year follow-up	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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485 **Table 9. Renal function at 3 months and 1 year**

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

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

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Figure 1. GDFT protocol for SV optimisation

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

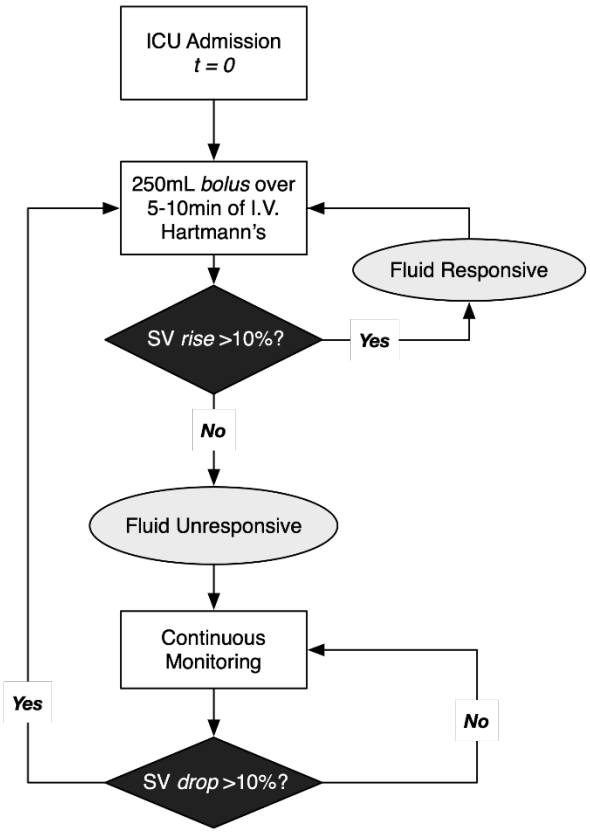


Figure 2. Study CONSORT flow diagram

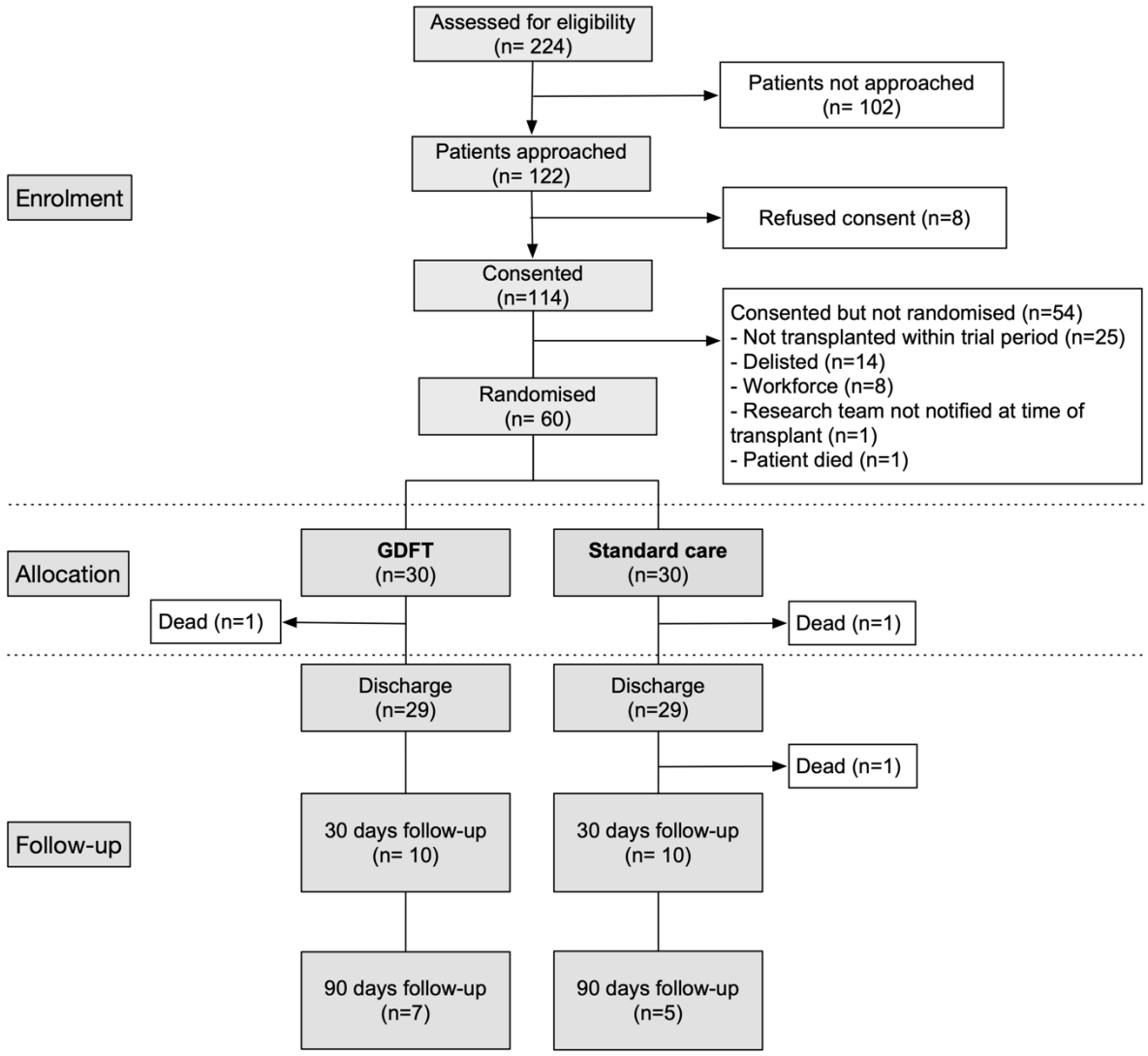
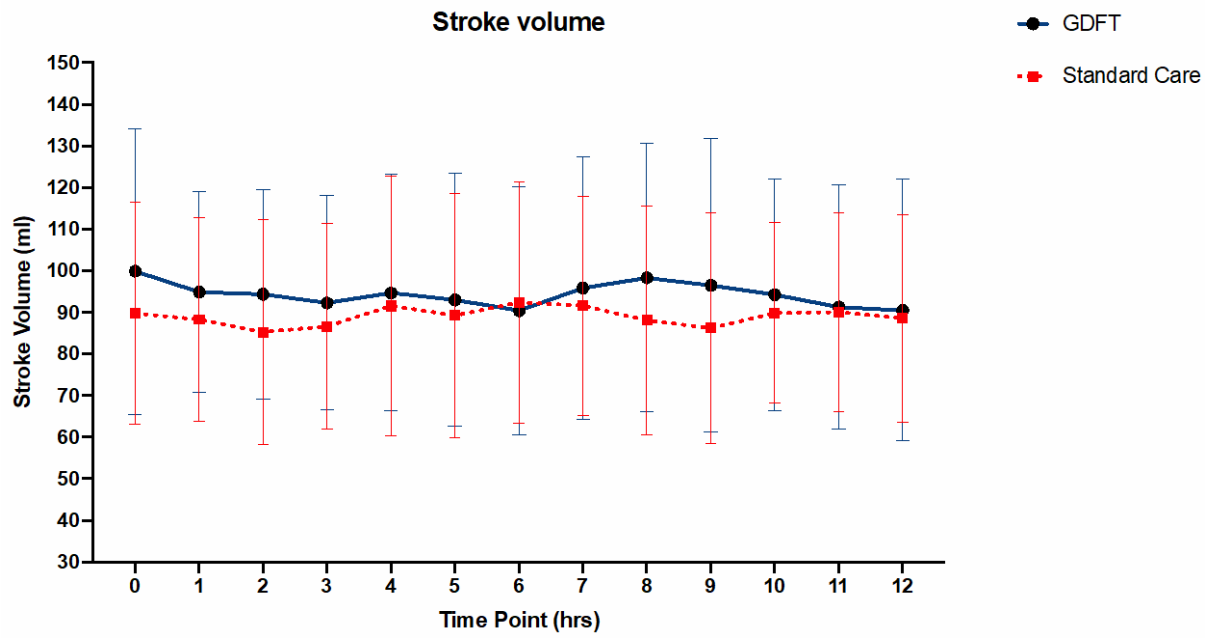
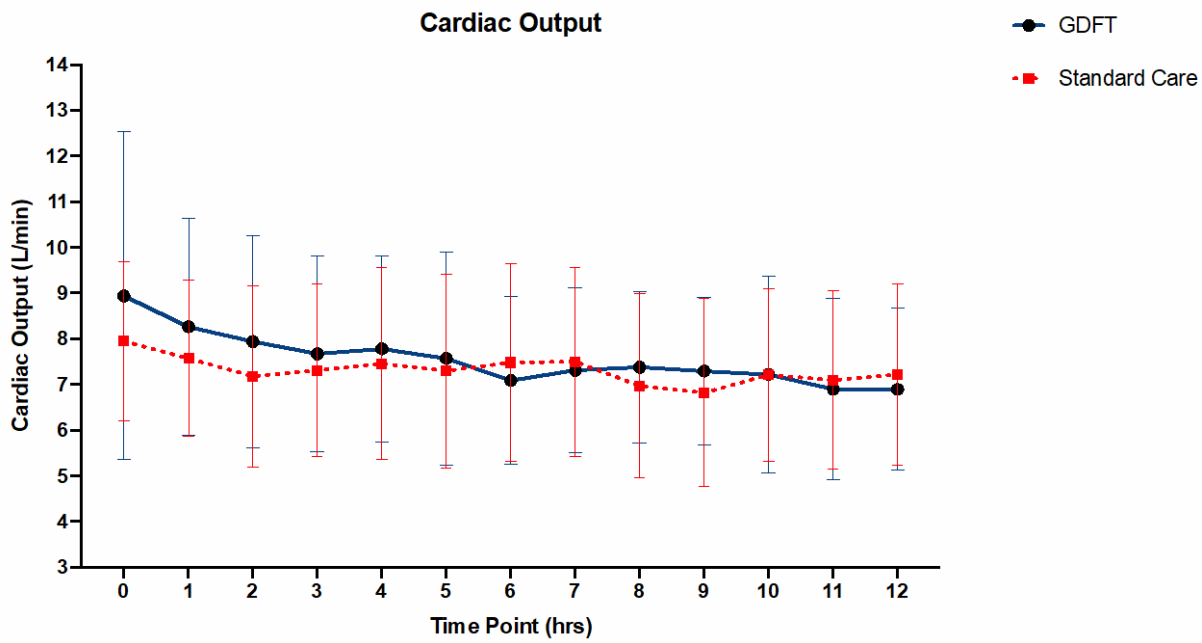


Figure 3. Stroke Volume



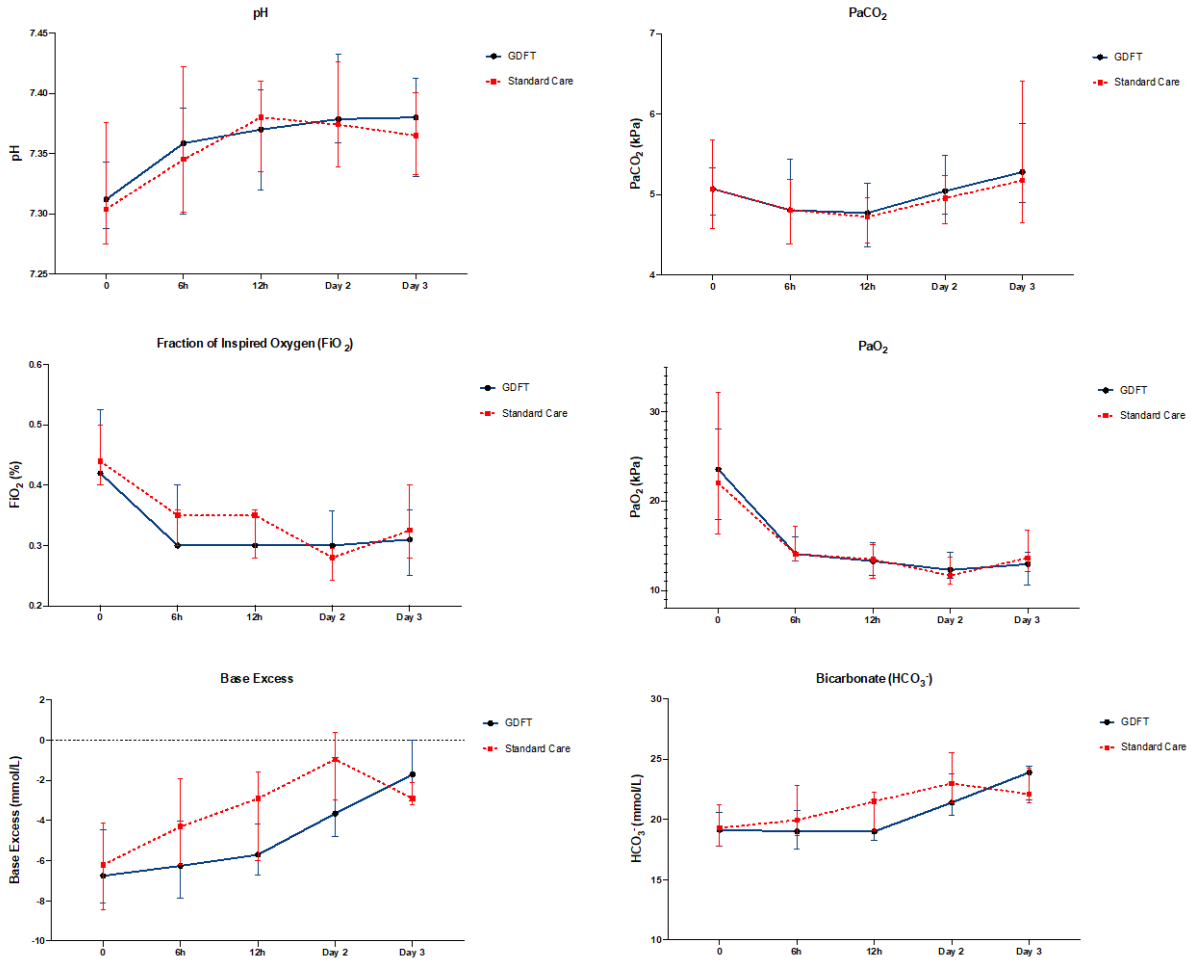
Mean profile plot with 95% CI

Figure 4. Cardiac Output



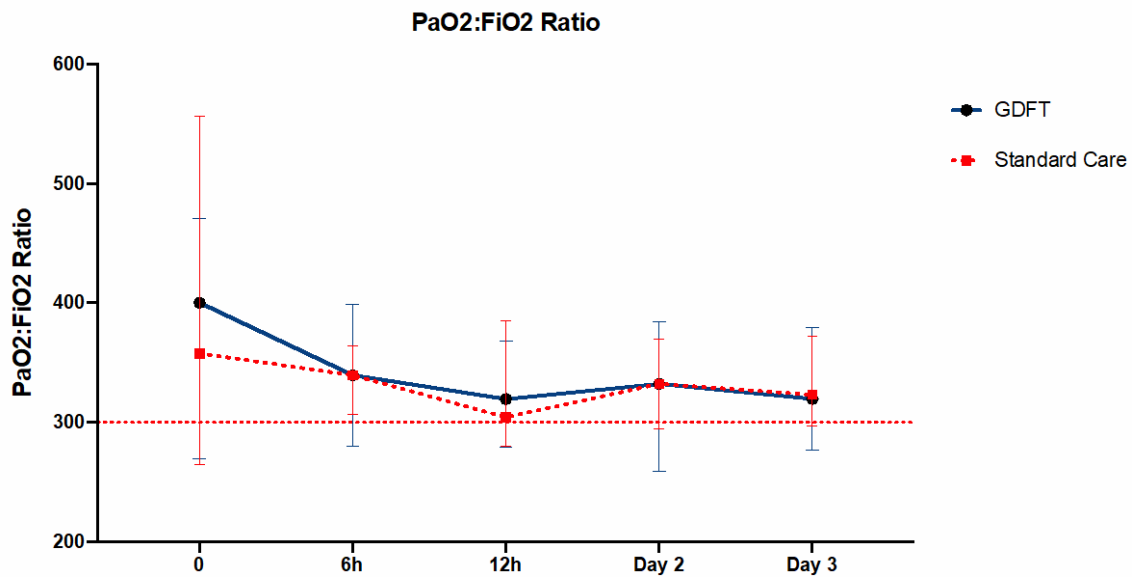
Mean profile plot with 95% CI

Figure 5. Arterial Blood Gas (ABG) parameters



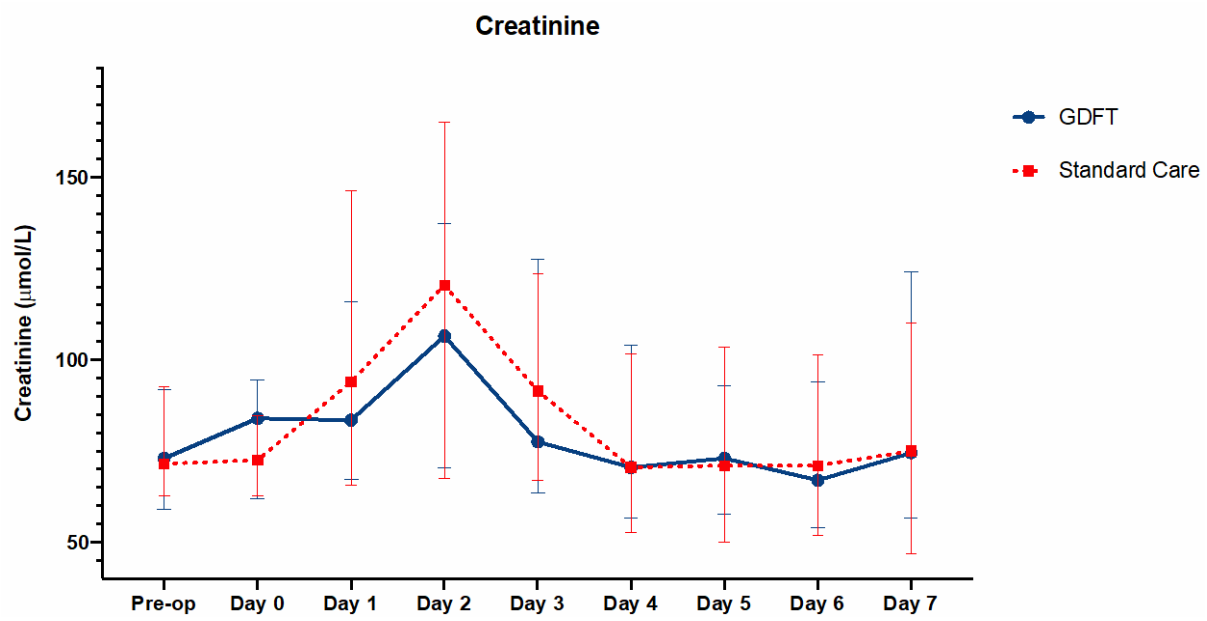
Mean profile plots with 95% CI

Figure 6. PaO_2:FiO_2 ratios



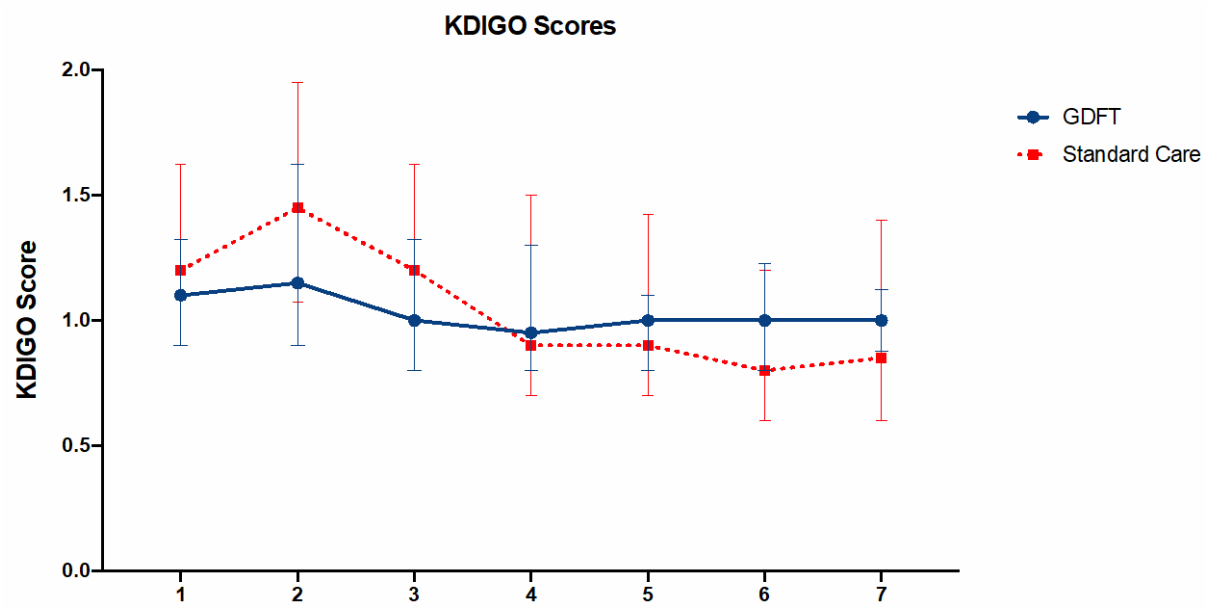
PaO_2:FiO_2 < 300 is consistent with ALI (acute lung injury) or mild ARDS.

Figure 7. Serum Creatinine



Mean profile plot with 95% CI

Figure 8. KDIGO scores



Mean profile plot with 95% CI