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Impact of intensive care on renal function before graft harvest:

results of a monocentric study

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Abstract

Background: The aim of life-support measures in brain-dead donors is to preserve the functional value of their organs. In renal transplantation, serum creatinine level is one of the criteria for graft harvest. The aim of this study was to assess the impact of intensive care on donor renal function through two criteria: preharvesting serum creatinine level above 120 µmol/L and the elevation of serum creatinine level above 20% between intensive care unit (ICU) admission and graft harvest.

Methods: Between January 1, 1999 and December 31, 2005, we performed an observational study on 143 brain-dead donors. ICU chronology, hemodynamic, hematosis, and treatment data were collected for each patient from ICU admission to kidney removal.

Results: Twenty-two percent of the 143 patients had a serum creatinine level above 120 µmol/L before graft harvest. The independent factors revealed by multivariate analysis were: the administration of epinephrine (OR: 4.36, CI 95%: 1.33-14.32, $p = 0.015$), oliguria (OR: 3.73, CI 95%: 1.22-11.36, $p = 0.021$), acidosis (OR: 3.26, CI 95%: 1.07-9.95, $p = 0.038$), the occurrence of disseminated intravascular coagulation (OR: 3.97, CI 95%: 1.05-15.02, $p = 0.042$), female gender (OR: 0.13, CI 95%: 0.03-0.50, $p = 0.003$), and the administration of desmopressin (OR: 0.12, CI 95%: 0.03-0.44, $p = 0.002$). The incidence of elevated serum creatinine level above 20% between admission and graft harvest was 41%. The independent risk factors were: the duration of brain death > 24 hours (OR: 2.64, CI 95%: 1.25-5.59, $p = 0.011$) and the volume of mannitol (OR: 2.08, CI 95%: 1.03-4.21, $p = 0.041$).

Conclusion: This study shows that the resuscitation of brain-dead donors impacts on their renal function. The uses of epinephrine and mannitol are associated with impairment of kidney function. It seems that graft harvest should be performed less than 24 hours after brain death diagnosis.

Introduction

The success of organ transplantation depends on the quality of the resuscitation of donors [1]. However, its renal impact has not been subject to much evaluation up to the present. To the best of our knowledge, no studies have evaluated the impact of the resuscitation on the preharvesting renal function of potential brain-dead donors. It seems interesting to know the risk factors for renal function impairment in such patients, since this can affect the future renal graft. Consequently, the primary objective of the present study was to assess the risk factors for renal impairment defined by a serum creatinine level above 120 µmol/L in a cohort of brain-dead donors. The secondary objective was to evaluate the risk factors for renal function deterioration, defined by a more than 20% rise of serum creatinine levels between intensive care unit (ICU) admission and graft harvest.

Patients and methods

Between January 1st, 1999 and December 31, 2005, a retrospective observational study was conducted on 143 among 150 brain-dead donors admitted to a 16-bed medico-surgical ICU of a 800-bed university hospital (Hôpital Nord, Marseille, France) (Figure 1). Informed consent and approval by the Ethics Committee were waived due to observational nature of the study.

Computer data were collected prospectively by the physicians upon admission and during ICU stay. Physicians met weekly to complete the data after discharged. During data extraction, a software program performed a final checking by eliminating aberrant values and suppressing duplications. The rate of uncompleted files was 5% (missing data > 5%). The patients with uncompleted files were excluded from the study. When the rate of missing data was <5%, they were ignored.

Donor resuscitation was performed according to the standard clinical practices. Diagnosis of brain death was confirmed by the presence of a profound coma (flaccid, hypotonic, areactive) with no cerebral trunk reflex and absence of ventilatory movement in a hypercapnic patient ($PaCO_2$ > 60 mmHg) [2]. In accordance with French legislation, clinical diagnosis was confirmed by two electroencephalograms performed at least four hours apart, or by angiography. As soon as the clinical diagnosis of brain death was confirmed, donor intensive care was performed according to French Society of Anesthesia and Intensive Care guidelines [3]. A written protocol, which is extracted from these guidelines was distributed to all the medical staff of our ICU.

Serum creatinine level is the most universal biological marker for estimating the glomerular filtration with a good prognostic value. Preharvesting serum creatinine level is considered to be important determinant of renal function after transplantation [4]. Hence, the present study evaluated the impact of the resuscitation of brain-dead donors on renal function. The primary objective was to assess the risk factors associated with a preharvesting serum creatinine level above 120 μmol/L. In order to better characterize the impact of care provided in ICU, the secondary objective was to identify the risk factors associated with a rise of more than 20% in serum creatinine levels between ICU admission and graft harvest. These two criteria have been reported in article analyzing preoperative risk factors for acute postoperative renal failure [5, 6]. The present study evaluated the influence of these two criteria on the renal graft quality through four criteria: delayed graft function, early acute rejection, return in dialysis (one month, one year), mortality (one year). Delayed graft function was defined by the need for dialysis in the seven days after transplantation [7]. Acute rejection of the renal allograft was defined by an elevation of serum creatinine levels of more than 20% between two successive measurements confirmed by a second biologic screening and after elimination of another cause of graft dysfunction, which could be functional, toxic, urologic, or vascular.

Any suspicion of acute rejection was confirmed by a histologic examination [8]. Data from donors were analyzed from ICU admission to kidney harvest. The demographic (sex, age) data, causes of ICU admission, duration of ICU stay, duration of shock, duration of brain death (from the clinical diagnosis), drugs used during the ICU stay (fluid expansion, catecholamines, osmotherapy, diuretics, desmopressin), hemodynamic profile during ICU resuscitation, characteristics of renal function on admission and during ICU stay with special interest in oliguria (defined by urine output < 0.5 mL/kg/h for at least two consecutive hours) and creatinine serum levels were collected. Catecholamines have been used alone or in combination, as required, according to the attending physician.

Biological disseminated intravascular coagulation is defined by elevated D-Dimers (D-Dimers greater than 500 µg/L) and one major criterion for consumption of platelets or coagulation factors (platelet count less than 50,000 mm^{-3} or international normalized ratio of the prothrombin time greater than 1.5) or two minor criteria for consumption of platelets or coagulation factors (platelet count between 50 and 100,000·mm^{-3} and international normalized ratio of the prothrombin time between 1.2 and 1.5) [9]. Shock was defined by hypotension (systolic blood pressure less than 90 mmHg or a mean arterial pressure less than 65 mmHg) not reversed with fluid resuscitation and serum lactate level above 3 mmol/L [10].

The collected data were entered into a Microsoft® Office Excel 2000, then transferred to SPSS v.11.5.1.® software for analysis of the results. Statistical descriptions: quantitative variables are presented in the form of mean ± SD. Qualitative variables are expressed as percentages. For the univariate analysis, associations were sought between serum creatinine level above 120 µmol/L and a rise of more than 20% in serum creatinine levels between ICU admission and organ harvest and the factors collected during the study by Student's *t*-test or an analysis of variance for the quantitative variables and by Chi-square test or Fisher Exact test for the qualitative variables. For the multivariate analysis, the variables provided by univariate

analysis were put into a logistic regression model. The values of successive models were evaluated by the Hosmer and Lemeshow test. The threshold for significance of the statistical tests was set at 5%.

Results

Demographic characteristics and parameters of resuscitation are shown in Table 1. The age of patients was 38 ± 14 years. Male represented 62% of the study population. Head trauma (49%) and spontaneous intracranial bleeding (40%) accounted for the most frequent causes of death. Among these 143 donors, 31 (22%) had a serum creatinine concentration above 120 µmol/L. The significant risk factors associated with preharvesting serum creatinine level above 120 µmol/L are summarized in Table 1. The occurrence of disseminated intravascular coagulation, the occurrence of cardiac arrest, shock, or acidosis were statistically associated with a serum creatinine level above 120 µmol/L. For catecholamines, the use of epinephrine was associated with a serum creatinine level above 120 µmol/L. Substitutive opotherapy by desmopressin had no adverse effect on renal function. As shown in Table 2, six independent risk factors were retained by the logistical regression model (Hosmer-Lemeshow statistic: 0.96, with 85.3% of patients correctly identified by the model). The use of epinephrine during the donor resuscitation, the occurrence of oliguria, acidosis, and disseminated intravascular coagulation were significantly associated with a preharvesting serum creatinine level above 120 µmol/L. On the other hand, the administration of desmopressin and female gender were negatively correlated with a preharvesting serum creatinine level above 120 µmol/L. The rate of delayed graft function was significantly increased in the recipients from the donors with a serum creatinine level above 120 µmol/L, as compared with those from donors with a serum creatinine level below 120 µmol/L. By contrast, there were no differences in the rates of acute rejection, return to dialysis, and mortality (Table 3).

A rise of more than 20% in serum creatinine levels between ICU admission and graft harvest was observed in 58 (41%) patients (Table 4). This rise was detected in the patients who were treated with large volume of mannitol (276 ± 241 mL versus 123 ± 221 mL, $p = 0.003$), in whom the duration of brain death was above 24 hours (76% versus 53%, $p = 0.006$), and in whom an iodinated radiographic contrast was injected (78% versus 61%, $p = 0.04$). When applying multivariate logistic regression analysis (Hosmer-Lemeshow statistic: 0.95 with 64.1% of the patients correctly identified by the model), the volume of mannitol infused during the initial resuscitation (OR: 2.08, CI 95%: 1.03-4.21, $p = 0.04$) and duration of brain death > 24 hours (OR: 2.64, CI 95%: 1.25-5.59, $p = 0.01$) were associated with rise of more than 20% in serum creatinine concentrations. The rise of more than 20% in serum creatinine levels was not associated with significant changes in the rates of delayed graft function, acute rejection, return to dialysis, and mortality (Table 3).

Discussion

To the best of our knowledge, no studies have compared the impact of resuscitation on renal function before graft harvest. Brain death is associated with complex hemodynamic, endocrine, and metabolic dysfunction that can lead to major complications with the potential donor. Untreated, this can progress to cardiovascular collapse with loss of valuable organs for transplantation. However, drugs used have an adverse potential effect on preharvesting renal function.

The present study confirms that elevated preharvesting serum creatinine levels are associated with an increased rate of delayed graft function [11]. Hence, we sought to determine the factors associated with a serum creatinine levels above 120 µmol/L in the donors. The administration of epinephrine is an independent risk factor associated with a rise in serum creatinine level above 120 µmol/L. This risk factor has not been previously described. The

use of epinephrine induces a renal vasoconstriction [12]. This can also reflect a profound state of hemodynamic instability. In agreement with our result, a recent study shows that the use of epinephrine in donors is associated with a negative influence on the graft quality after transplantation [13].

The occurrence of disseminated intravascular coagulation is an independent risk factor associated with a serum creatinine level above 120 µmol/L. The link between hemostasis and brain injury has been reported elsewhere [14]. In cases of cerebral injury, one can observe central hyperthermia owing to the lack of thalamic regulation which can activate coagulation and result in disseminated intravascular coagulation [15]. Also, the occurrence of acidosis is an independent risk factor, probably reflecting a cellular dysoxia.

The occurrence of oliguria is an independent risk factor associated with a serum creatinine concentration above 120 µmol/L. Oliguria can be a marker of hemodynamic instability or acute renal failure. This risk factor has been already described in recipients but not in donors [16]. Oliguria, whatever its significance, should be avoided in potential donors. However, in our study, the volume of fluid resuscitation did not impact on the value of preharvesting serum creatinine level. This suggests that an aggressive volume resuscitation in order to avoid oliguria is not always associated with a clinical success.

Administration of desmopressin was inversely correlated with the occurrence of a serum creatinine level above 120 µmol/L. The effects of desmopressin on graft function are variable and several studies have reported no changes in renal function [17]. By contrast, the impact on pancreas grafts is deleterious with microthromboses and loss of function [18]. One possible protective mechanism at the renal level may be a vasodilatation obtained via the activation of V2-receptors. Indeed, desmopressin induces a vasodilatation via the production of nitric oxide [19].

Although the admission serum creatinine levels are significantly higher in the group with a preharvesting serum creatinine level above 120 µmol/L, this factor is not found as an independent risk factor. By contrast, the lower preharvesting serum creatinine level in females can be the consequence of their lower muscle mass. The analysis of estimated glomerular filtration rate instead of serum creatinine levels would lift this ambiguity.

A rise of more than 20% in serum creatinine levels between ICU admission and graft harvest, with an incidence of 41%, is associated with a duration of brain death > 24 hours. A prior study found that the duration of resuscitation does not influence the quality of kidney grafts transplanted if the hemodynamic condition of the donor is maintained [20]. However, the link between the quality of kidney graft and the ICU length of stay appears to be complex. It has been shown that a donor prolonged ICU stay is correlated with a lower risk of delayed graft function in the recipients [13]. Regarding our results, a long duration of ICU stay before the occurrence of brain death does not affect the quality of kidney, whereas a prolonged duration of brain death may impair the preharvesting renal function. Hence, the duration of brain death should be shortened as much as possible in order to preserve the renal function.

This rise is also associated with the use of large volume of mannitol. Mannitol increases urine output but it does not reduce the incidence of acute renal failure [21]. Cases of acute renal failure can be encountered in relation to mannitol serum levels that are too high [22, 23]. One hypothesis is that mannitol infusion could generate osmotic nephrosis-like lesions with a direct nephrotoxic effect [24]. Interestingly, use of hypertonic saline solution, which is an alternative to mannitol [25], is not associated with a worsening of renal function in our patients.

We acknowledge that the present study has several limitations. The retrospective design limits the interpretation of data. In addition, the patients were hospitalized in a single institution, which reflects a local policy of management of donors. Lastly, we used a criteria to define the

worsening of renal function which is not precisely described in the literature in the field of renal transplantation. In fact, the definition of acute renal failure is far from consensus [26]. One can note that our criteria for evaluating renal function are restrictive.

Conclusion

In summary, within the limitations of this study, the use of epinephrine in the potential donors is associated with an increased risk (x 4.3) of preharvesting serum creatinine level above 120 µmol/L. A large volume of mannitol is associated with an increased risk (x 2) of rise of more than 20% in serum creatinine levels between ICU admission and graft harvest, whereas the use of hypertonic saline solutions do not share this negative effect. Importantly, although the duration of ICU stay prior brain death occurrence has no impact on the preharvesting renal function, the procedure of transplantation should be fast as soon as the brain death is detected. Lastly, administration of desmopressin is associated with a preservation of renal function. This result deserves to be investigated in further prospective studies.

Key messages

- The present study was aimed at assessing the impact of intensive care on donor renal function.
- The use of epinephrine in the potential donors is associated with an increased risk (x 4.3) of preharvesting serum creatinine level above 120 µmol/L.
- A large volume of mannitol is associated with an twofold risk of a rise of more than 20% in serum creatinine levels between ICU admission and graft harvest, whereas the use of hypertonic saline solutions do not share this effect.

- Although the duration of ICU stay prior brain death occurrence has no impact on the preharvesting renal function, the procedure of transplantation should be fast as soon as the brain death is detected.
- Administration of desmopressin is associated with a preservation of renal function.

Author's contributions

JA and CM conceived and supervised the study, interpreted results, and drafted the manuscript.

VB and ML conducted searches, abstracted data, corresponded with authors, analyzed and interpreted results, and edited the manuscript.

AG provided data on the recipient kidney function.

JB advised on statistical analyses, interpreted results, and drafted the manuscript.

Competing interests

The authors declare that they have no competing interests**.**

List of abbreviations

CI: Confidence interval

h: hours

ICU: intensive care unit

MAP: mean arterial pressure

min: minutes

n: number

OR: Odd-ratio

$PaCO_2$: arterial partial pressure of carbon dioxide

SD: Standard deviation

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Table 1. Factors for preharvesting serum creatinine level > 120 µmol/L (*$p < 0.05$)

	All Patients (n=143)	Preharvesting creatinine	
		< 120 µmol/L (n=112)	> 120 µmol/L (n=31)
Demographic data			
Women n, (%)	54 (38)	50 (45)	4 (13)*
Age (years) (mean ± SD)	38 ± 14	38 ± 13	39 ± 15
Causes of ICU admission			
Head trauma n, (%)	70 (49)	50 (45)	20 (65)*
Intracranial bleeding n, (%)	57 (40)	53 (47)	4 (13)*
Cerebral anoxia n, (%)	8 (5.5)	4 (3.5)	4 (13)
Suicide n, (%)	8 (5.5)	5 (4.5)	3 (10)
ICU steps			
Duration of stay in ICU (h) (mean ± SD)	70 ± 64	76 ± 66	49 ± 48*
Duration of brain death (h) (mean ± SD)	30 ± 14	29 ± 12	33 ± 18
Duration of brain death > 24 h (%)	58 (41)	50 (44)	8 (26)
Catecholamines			
Dopamine n, (%)	37 (26)	32 (29)	5 (16)
Dobutamine n, (%)	11 (8)	10 (9)	1 (3)
Epinephrine n, (%)	51 (36)	31 (28)	20 (64)*
Norepinephrine n, (%)	101 (71)	80 (71)	21 (68)
Fluid expansion			
Isotonic saline solution (mL) (mean ± SD)	3655 ± 4003	3667 ± 4247	3612 ± 3015
Lactate ringer (mL) (mean ± SD)	2582 ± 2598	2665 ± 2633	2280 ± 2483
Gelatin (mL) (mean ± SD)	446 ± 928	466 ± 971	370 ± 763
Hydroxyethylstarch n, (%)	113 (79)	86 (77)	27 (87)
Hydroxyethylstarch (mL) (mean ± SD)	1170 ± 1080	1140 ± 1100	1274 ± 1015
Osmotherapy			
Mannitol 20% (mL) (mean ± SD)	185 ± 285	200 ± 301	132 ± 215
Hypertonic saline solution 7.5% (mL) (mean ± SD)	131 ± 296	130 ± 281	130 ± 351
Urine output modulators			
Furosemide n, (%)	36 (25)	30 (27)	6 (19)
Furosemide (mg) (mean ± SD)	16 ± 51	16 ± 56	12 ± 28
Desmopressin n, (%)	114 (80)	98 (87)	16 (52)*
Desmopressin (µg) (mean ± SD)	5.9 ± 5.7	6.8 ± 6.1	2.7 ± 3*
Hemodynamic profile during ICU resuscitation			
Cardiac arrest n, (%)	26 (18)	14 (12)	12 (39)*
Shock n, (%)	93 (65)	67 (60)	26 (83)*
Duration of shock (min) (mean ± SD)	80 ± 142	61 ± 104	150 ± 223*
MAP upon admission (mmHg) (mean ± SD)	89 ± 25	93 ± 23	75 ± 26*
Preharvesting MAP (mmHg) (mean ± SD)	81 ± 17	82 ± 18	77 ± 16
Respiratory profile during ICU resuscitation			
Acute respiratory distress syndrome n, (%)	53 (37)	37 (33)	16 (52)
Acute lung injury n, (%)	33 (23)	30 (27)	3 (10)*
Characteristics of renal function			
Oliguria n, (%)	66 (46)	44 (39)	22 (71)*
Serum creatinine upon admission (µmol/L) (mean ± SD)	89 ± 38	79 ± 26	125 ± 49*
Preharvesting serum creatinine (µmol/L) (mean ± SD)	98 ± 61	75 ± 21	180 ± 83*
Acidosis (pH < 7.30) n, (%)	45 (31)	24 (21)	21 (68)*
Disseminated intravascular coagulation n, (%)	24 (17)	13 (12)	11 (35)*
Injection of contrast n, (%)	97 (68)	77 (69)	20 (64)

ICU: intensive care unit; MAP: mean arterial pressure; n: number; SD: standard deviation

Table 2. Independent risk factors for preharvesting serum creatinine level > 120 µmol/L

	p	OR	CI 95%
Epinephrine use	0.015	4.36	1.33-14.32
Disseminated intravascular coagulation	0.042	3.97	1.05-15.02
Oliguria	0.021	3.73	1.22-11.35
Acidosis	0.038	3.26	1.07-9.95
Female gender	0.003	0.13	0.03-0.50
Desmopressin use	0.002	0.12	0.03-0.44

Table 3. Kidney complications after transplantation (*$p < 0.05$)

Complications	All patients (n = 233)	Preharvesting serum creatinine > 120 µmol/L (n = 51)	Elevated serum creatinine > 20% (n = 94)
Delayed graft function n, (%)	88 (38)	29 (57)*	35 (37)
Acute rejection n, (%)	36 (15.5)	9 (8)	19 (20)
Return in dialysis at one month n, (%)	8 (3.4)	2 (4)	2 (2.1)
Return in dialysis at one year n, (%)	14 (6)	3 (6)	4 (4.3)
Mortality at one year n, (%)	6 (2.6)	4 (7.8)	2 (2.1)

Table 4. Factors for an elevation of serum creatinine levels of 20% or more (*$p < 0.05$)

	Elevation of serum creatinine levels	
	< 20 % (n = 85)	**> 20 % (n = 58)**
Demographic data		
Women n, (%)	36 (42)	18 (31)
Age (years) (mean ± SD)	39 ± 14	38 ± 13
Causes of ICU admission		
Head trauma n, (%)	37 (43)	33 (57)
Intracranial bleeding n, (%)	37 (44)	20 (36)
Cerebral anoxia n, (%)	6 (8)	2 (3)
Suicide n, (%)	5 (6)	3 (5)
ICU steps		
Duration of stay in ICU (h) (mean ± SD)	63 ± 56	80 ± 72
Duration of brain death (h) (mean ± SD)	27 ± 11	34 ± 17*
Duration of brain death > 24 h n, (%)	45 (53)	44 (76)*
Catecholamines		
Dopamine n, (%)	26 (31)	11 (19)
Dobutamine n, (%)	5 (6)	6 (10)
Epinephrine n, (%)	28 (33)	23 (40)
Norepinephrine n, (%)	58 (68)	43 (74)
Fluid expansion		
Isotonic saline solution (mL) (mean ± SD)	3406 ± 3825	4020 ± 4259
Lactate ringer (mL) (mean ± SD)	2696 ± 2641	2413 ± 2546
Gelatin (mL) (mean ± SD)	441 ± 930	452 ± 933
Hydroxyethylstarch n, (%)	67 (79)	46 (79)
Hydroxyethylstarch (mL) (mean ± SD)	1047 ± 1019	1349 ± 1148
Osmotherapy		
Mannitol 20 % (mL) (mean ± SD)	123 ± 221	276 ± 241*
Hypertonic saline solution 7.5% (mL) (mean ± SD)	111 ± 235	159 ± 369
Urine output modulators		
Furosemide n, (%)	19 (22)	17 (29)
Furosemide (mg) (mean ± SD)	14 ± 57	17 ± 42
Desmopressin n, (%)	68 (80)	46 (79)
Desmopressin (µg) (mean ± SD)	5.7 ± 6.2	6.2 ± 5.1
Hemodynamic profile		
Cardiac arrest n, (%)	16 (19)	10 (17)
Shock n, (%)	53 (62)	40 (69)
Duration of shock (min) (mean ± SD)	65 ± 108	102 ± 180
MAP upon admission (mmHg) (mean ± SD)	91 ± 25	87 ± 25
Preharvesting MAP (mmHg) (mean ± SD)	81 ± 17	81 ± 18
Respiratory profile		
Acute respiratory distress syndrome n, (%)	22 (26)	23 (40)
Acute lung injury n, (%)	21 (25)	11 (19)
Characteristics of renal function		
Oliguria n, (%)	39 (46)	27 (47)
Serum creatinine upon admission (µmol/L) (mean ± SD)	95 ± 42	80 ± 28*
Preharvesting serum creatinine (µmol/L) (mean ± SD)	82 ± 40	121 ± 76*
Acidosis (pH < 7.30) n, (%)	23 (27)	22 (38)
Disseminated intravascular coagulation n, (%)	11 (13)	13 (22)
Injection of contrast n, (%)	52 (61)	45 (78)*

ICU: intensive care unit; MAP: mean arterial pressure; n: number; SD: standard deviation

Figure Legend

Figure 1- Flow-chart of the inclusion

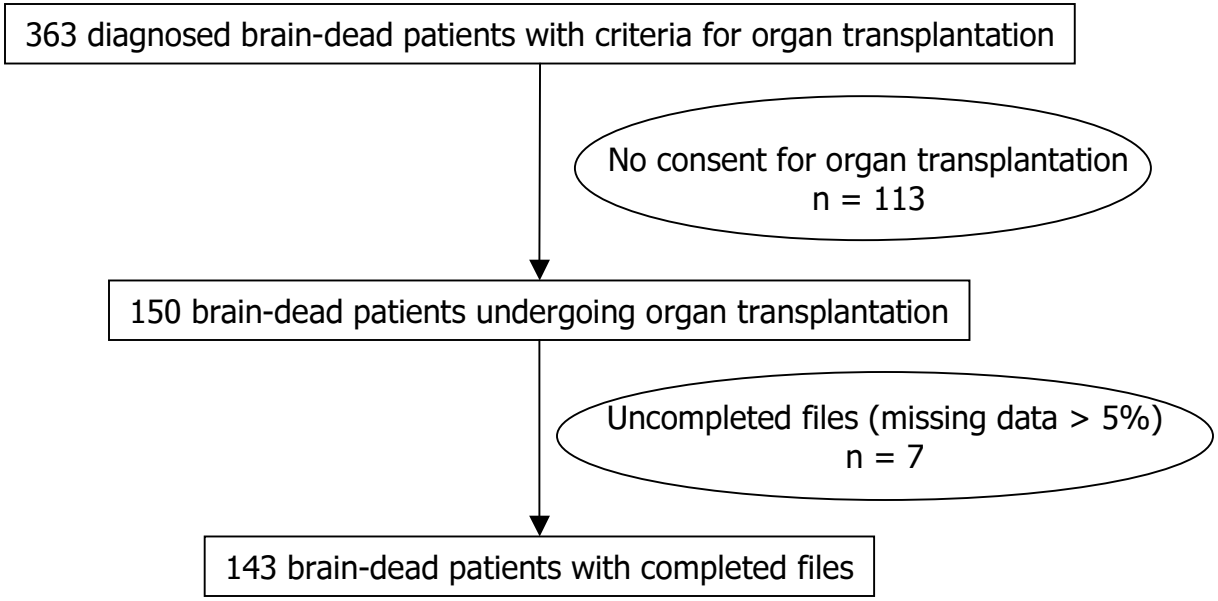
363 diagnosed brain-dead patients with criteria for organ transplantation
No consent for organ transplantation
n = 113
150 brain-dead patients undergoing organ transplantation
Uncompleted files (missing data > 5%)
n = 7
143 brain-dead patients with completed files

Figure 1