# Assessment of Neutrophil Gelatinase-associated Lipocalin in the Brain-dead Organ Donor to Predict Immediate Graft Function in Kidney Recipients

## *A Prospective, Multicenter Study*

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**ABSTRACT**

**Background:** Delayed graft function is a major determinant of long-term renal allograft survival. Despite considerable efforts to improve donor selection and matching, incidence of delayed graft function remains close to 25%. As neutrophil gelatinase-associated lipocalin (NGAL) has been shown to predict acute renal failure, the authors tested the hypothesis that NGAL measurement in brain-dead donors predicts delayed graft function in kidney recipients.

**Methods:** In a prospective, multicenter, observational study, serum NGAL was measured in donors at the time of transfer to operating room. The primary endpoint was the delayed graft function, defined as the need for renal replacement therapy during the first week posttransplantation.

**Results:** Among 159 included brain-dead donors, 146 were analyzable leading to 243 renal transplantations. Of these, 56 (23%) needed renal replacement therapy. Donors' NGAL values were similar in case of both delayed and normal graft function in recipients. The area under the receiver-operating curve for NGAL to predict the need for renal replacement therapy before day 8 was 0.50 (95% CI, 0.42 to 0.59). The area under curve for NGAL to predict failure to return to a normal graft function at day 8 was 0.51 (95% CI, 0.44 to 0.59). Using multivariate analysis, NGAL was not associated to the need for renal replacement therapy (odds ratio, 0.99; 95% CI, 0.98 to 1.00) or failure to return to a normal graft function at day 8 (odds ratio, 1.00; 95% CI, 0.99 to 1.00).

**Conclusion:** NGAL measurement in brain-dead donors at the time of recovery failed to predict delayed or normal graft function in kidney recipients. (**Anesthesiology** 2015; 122:96-105)

R ENAL transplantation is considered as the standard therapy for end-stage chronic kidney disease[1] because it allows a better quality of life with a lower cost than dialysis.[1,2] Although living donation has been shown as a valuable and safe response to shortage of organs for transplantation, a large majority of kidney transplantation is obtained from organ donation after brain death (BD).[3,4] Quality of donor care is a major determinant of graft success and increases the number of eligible donors.[5,6] Despite considerable efforts to improve quality of care for transplanted patients, 20 to 30% of delayed graft function (DGF, defined as a need for renal replacement therapy [RRT] within 8 days after transplantation) are usually reported after renal transplantation from deceased donors.[7–9] As early recovery of graft function

> **What We Already Know about This Topic**
> - Delayed graft function in renal transplant recipients still remains at 25%
>
> **What This Article Tells Us That Is New**
> - Despite the ability to predict acute renal failure earlier than serum creatinine rises in critically ill patients, neutrophil gelatinase-associated lipocalin measurements in blood samples obtained from brain-dead donors before kidney graft harvesting failed to predict either delayed or normal graft function in kidney recipients

determines long-term graft survival, DGF is a fundamental prognosis variable.[9,10] Expanded criteria for donors (ECD), especially age greater than 60 yr, could be a major explanation

for the high rate of DGF.[11,12] Nevertheless, if ECD influence graft success, some studies surprisingly report only a slight difference of graft prognosis obtained from standard criteria donors *versus* ECD.[7,11] These observations reflect the influence of other detrimental factors such as cold ischemic time, Human Leukocyte Antigen match, female sex, Caucasian origin,[11] and the global quality of donor management.[13] It has been demonstrated that cold ischemic time and DGF are two major factors of long-term renal allograft survival.[10] Because DGF rate remains high, obtaining new criteria to predict DGF could be of particular interest to detect occult renal failure in brain-dead[14] donors to improve donor–recipient matching. Recently, it was hypothesized that new biomarkers could better predict acute kidney injury (AKI) than classical markers such as serum creatinine or blood urea nitrogen.[15] The neutrophil gelatinase-associated lipocaline (NGAL) was identified as a 25 kDa polypeptide chain of 178 amino acids that belongs to the lipocalin family of proteins and is produced by polymorphonuclear neutrophil cells and predominantly by renal tubule epithelial cells.[16] In intensive care unit (ICU), NGAL predicts AKI 48 h earlier than serum creatinine and/or Risk, Injury, Failure, Loss, End-stage kidney disease classification[17] criteria.[18] The NGAL measurement could be also useful for assessing graft function after renal transplantation.[19–21] In contrast, NGAL has been poorly studied to assess occult renal dysfunction in BD donors. Only one previous study reported that both urinary NGAL (U-NGAL) and serum NGAL (S-NGAL) failed to predict DGF in 99 BD donors.[22] However, this previous study has several limitations: it was a monocentric study, with a potential center effect; measurement of S-NGAL was performed before the occurrence of BD in a significant proportion of patients (36%); and all patients were given glucocorticoids, which does not reflect the practice of all centers. These limitations justify a new multicenter study to clarify the usefulness of NGAL as biomarker in BD patients for predicting DGF in kidney recipients. Therefore, in the current study, we test the hypothesis that S-NGAL measurement in BD organ donors predicts DGF in kidney recipients.

## Materials and Methods

Considering that the current study was noninterventional and that such investigation did not need significant additional blood sample (volume <0.5 ml), the institutional review board approved this study (Institutional Review Board, Nîmes University Hospital, France, file number 2011.01.01) and stated that informed consent of next-of-kin was not required as organ donors are not considered human subjects. However, the next-of-kin was systematically orally informed and could refuse the participation. According to the French law, the National Committee on Health Research Data Analysis (*CCTIRS, Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé*, Nîmes France, file number: 11.140) and the National Committee on Information Technology (*Commission Nationale de l'Informatique et des Libertés*, Paris, France, file number EGY/FLR/AR114292) also approved this study. This prospective, multicenter, observational study was conducted by a French anesthesia and intensive care research network (AzuRea group). Patients were enrolled in 19 medical or surgical ICU of eight French teaching hospitals more than an 11-month period (February to December 2011). Data were anonymously collected using electronic case report form.

### Brain-dead Organ Donors

All BD patients in whom organ retrieval was performed were eligible. Clinical diagnosis of BD was performed with a strict adherence to the standard international criteria[23] and confirmed by either computed tomography angiography or electroencephalography, according to the French law. An interview of relatives and/or closest was systematically performed to confirm the absence of known refusal of the BD patients to organ donation; we also checked the French national registry of refusal of organ donation. Standard medical contraindications to organ donation were also checked. Patients in whom a contraindication to kidney donation was identified were excluded. In BD donors, the following variables were collected: age, sex, weight, height, medical history of cardiac failure (defined as New York Heart Association 3 or 4 classes), coronary artery disease, arterial hypertension, peripheral obliterating arterial disease, tobacco consumption (more than one pack per day during 20 yr), diabetes mellitus, hyperlipidemia (defined as chronic treatment for hypercholesterolemia or hypertriglyceridemia). The ECD for kidney were defined by the following elements: age older than 60 yr, age between 50 and 60 yr and one of the following risk criteria as arterial hypertension, stroke as a cause of BD, and at least one serum creatinine dosage greater than 130 µmol/l. The sepsis-related organ failure assessment score[24] was recorded at the time of NGAL sampling.

We recorded mean arterial blood pressure (mmHg), heart rate (beats/min), at the time of transfer to the operating room and the worst value of mean arterial pressure during the 24 h before, urine output during the 6 and 12 h before transfer, the total amount and the type of fluids infused to donor during the 24 h before transfer, and the dose of norepinephrine administered at the time of transfer to the operating room. Serum creatinine and blood urea nitrogen, serum lactate, arterial blood gases, proteinuria, at the time of transfer to the operating room, and their worst values in the previous 48 h were also recorded.

### Sample Collection and NGAL Detection

To assess the whole period at risk for AKI before kidney harvesting, a blood sample (0.25 ml) was withdrawn just before entering into the operating room. Each center was equipped with a portable biological diagnostic device allowing NGAL assay in few minutes (Triage® MeterPro Meter; Biosite Inc., San Diego, CA). The NGAL measurements were performed

by fluorescence immunoassay specific kits (Triage® meter NGAL test, Alere, Jouy en Josas, France). The range of quantification was 60 to 1,300 ng/ml. For this technique, the reported variation coefficient was 10 to 15%.

### Kidney Recipients

Assessment of renal function in kidney recipients was based on data obtained from the different transplantation units during the first postgraft week. DGF was the primary endpoint and was defined as any RRT before day 8 (D8) posttransplantation.[25] The secondary endpoint was the failure to return to a normal graft function. A normal graft function was defined as urine output greater than 1,000 ml/day and serum creatinine less than 167 μmol/l during 2 consecutive days at D8 posttransplantation.[12,25] We also recorded cold ischemic time defined as the time from aortic clamping in donor and graft declamping in recipient for each transplanted kidney.

### Statistical Analysis

All statistical analyses were performed using SAS© (SAS Institute, Cary, NC) version 9.3. Quantitative variables were expressed as median with 25th and 75th percentiles and compared using Mann–Whitney tests. Qualitative variables were expressed as proportions and compared using chi-square tests (or Fisher exact tests when appropriate). Receiver operator characteristic curves were generated to evaluate the capacity of NGAL to predict DGF and failure to return to a normal graft function. A logistic mixed model with three hierarchical levels was used with a center random effect and a donor random effect within each center to take into account the link between the two transplanted kidneys from the same donor. Univariate and multivariate analyses were successively performed to assess the capacity of NGAL to predict DGF by adjusting on other expected predictors such as cold ischemic time, ECD, serum creatinine.

The sample size calculation was based on a previous study conducted by our group in which we found a proportion of DFG of 30%.[26] We tested the hypothesis that NGAL is a significant predictor of dialysis before D8 posttransplantation, that is, that it could predict RRT with a value of area under the receiver operator characteristic curve of 0.82 and accuracy precision of 0.07 (keeping the lower value of the CI >0.75).[27] We calculated that 132 patients were required, to be conservative we decided thus to enroll at least 150 patients.

All $P$ values were two tailed and a $P$ value less than 0.05 was considered significant.

## Results

During the study period, 159 BD patients with renal donation were included. Characteristics of BD patients and their management are shown in table 1. Figure 1 shows study flow chart. Dosage of S-NGAL was not performed for 13 patients leading to 146 analyzable BD donors that could have theoretically led to 292 renal transplantations (fig. 1). Finally, 29 transplants were not grafted and 20 recipients were not assessed for renal function at D8, for a total of 243 transplants assessable for primary and secondary endpoints. The mean cold ischemic time in recipient population was 14.5 (12 to 19) h.

Among 243 recipients (115 and 128 right and left transplants, respectively), 56 (23%) needed RRT before D8 after graft. The median S-NGAL value was similar in case of RRT requirement or not (103 [60 to 300] *vs.* 102 [60 to 260] ng/ml, $P$ = 0.94). The distribution of S-NGAL values was strictly comparable in case of DGF as compared to those without DGF (fig. 2A). The AUC of S-NGAL for predicting RRT in recipients was 0.50 (95% CI, 0.42 to 0.59) (fig. 2B). The AUC of serum creatinine measured at the same time was 0.60 (95% CI, 0.53 to 0.67). At D8, multivariate analysis showed that S-NGAL was not significantly associated to DGF, whereas a 1-h longer cold ischemic time and a 10 μmol/l increase in creatinine plasma value were both significantly associated to DGF (table 2).

Among the 243 recipients, 112 (46%) failed to return to a normal graft function at D8. The S-NGAL dosage were similar in case of normal graft function or not (102 [60 to 226] *vs.* 106.5 [60 to 317.5] ng/ml, $P$ = 0.69). The distribution of S-NGAL values between recipients with normal graft function or not was similar (fig. 3A). The AUC the receiver operator characteristic curve of NGAL for predicting the failure to return to a normal graft function at D8 was 0.51 (95% CI, 0.44 to 0.59) (fig. 3B). In the logistic mixed model, S-NGAL was not predictive of failure to return to a normal graft function, whereas a longer cold ischemic time and an increase in creatinine plasma value were both significantly predictive of failure to return to a normal graft function at D8 (table 3).

For the need of RRT at day 8, the logistic mixed model showed no significant impact center effect ($P$ = 0.17) or no significant impact of the link between the two transplanted kidneys from the same donor ($P$ = 0.29). For the return to normal renal function at day 8, the logistic mixed model showed no significant impact center effect ($P$ = 0.26) or no significant impact of the link between the two transplanted kidneys from the same donor ($P$ = 0.06).

## Discussion

In the current prospective multicenter study, NGAL measurement in BD organ donors failed to predict DGF or normal graft function in kidney recipients. Cold ischemic time and an increase in serum creatinine in BD donor were significantly associated to DGF.

NGAL is one of the most promising and studied AKI biomarkers.[15,28] In healthy subjects, proximal and distal tubular epithelial cells synthesize and secrete low levels of NGAL that are detectable in plasma. An extra-renal production of NGAL (gut, bone marrow, and lungs) also participates to NGAL plasma level. In the glomerulus, plasma NGAL is rapidly filtered. The filtered NGAL is largely

**Table 1.** Characteristics of Brain-dead Donors (n = 159)

| Variables | Values |
|---|---|
| Women | 59 (37%) |
| Men | 100 (63%) |
| Age (yr) | 53 (38–62) |
| Weight (kg) | 72 (63–81) |
| Height (cm) | 172 (165–179) |
| Medical history | |
|   Chronic cardiac failure or coronary artery disease (missing data = 3) | 11 (7%) |
|   Hypertension | 37 (23%) |
|   Peripheral vascular occlusive arteriopathy (missing data = 3) | 2 (1%) |
|   Diabetes mellitus | 13 (8%) |
|   Dyslipidemia | 15 (9%) |
|   Smoker | 46 (29%) |
| Cause of brain death | |
|   Stroke | 84 (53%) |
|   Traumatic brain injury | 57 (36%) |
|   Cardiac arrest | 12 (8%) |
|   Others | 6 (4%) |
| SOFA score | 10 (9–12) |
| Maximal creatinine in the last 48 h before operating room (μmol/l) | 90 (68–115) |
| Maximal urea in the last 48 h before operating room (mmol/l) | 6.0 (4.7–8.4) |
| Urine output in the last 12 h before operating room (ml kg$^{-1}$ h$^{-1}$) | 1,700 (1,100–2,500) |
| Urine output in the last 6 h before operating room (ml kg$^{-1}$ h$^{-1}$) | 775 (485–1,200) |
| Vasoactive drugs (missing data = 11) | |
|   Norepinephrine | 145 (98%) |
|   Dobutamine | 15 (10%) |
|   Dopamine | 7 (5%) |
|   Terlipressine | 2 (1%) |
| Time from ICU admission to brain death diagnosis (days) | 2 (1–3) |
| Time from brain death to aorta clamping (h) | 14 (10–17) |
| Blood lactates at time of operating room (mmol/l) | 1.6 (1.1–2.2) |
| Heart rate (beats/min) | 94 (82–112) |
| Minimal mean arterial pressure in the last 24 h before operating room (mmHg) | 66 (60–74) |
| Mean arterial pressure just before the transfer to operating room (mmHg) | 85 (76–96) |
| Norepinephrine posology before the transfer to operating room (mg/h) | 1.78 (1.00–3.6) |
| Arterial pH before the transfer to operating room | 7.40 (7.30–7.44) |
| Arterial Po$_2$ before the transfer to operating room (mmHg) | 309 (177–398) |
| Arterial Pco$_2$ before the transfer to operating room (mmHg) | 37 (32–44) |
| Proteinuria before the transfer to operating room (g/l) | 0.20 (0.10–0.52) |
| Cristalloids in the last 24 h before operating room | 3,000 (2,000–4,000) |
| Colloids in the last 24 h before operating room | 500 (0–1,000) |
| NGAL (ng/ml) (13 missing data) | 108.5 (60.0–285.0) |

Results are expressed as n (%) or median (25th percentile–75th percentile).
ICU = intensive care unit; NGAL = neutrophil gelatinase-associated lipocalin; SOFA = Sequential Organ Failure Assessment.

reabsorbed by proximal tubule, *via* receptor binding (Megalin) and endocytosis. Therefore, in physiological conditions, NGAL is barely detectable in urine or plasma. In case of AKI with acute tubular injury, plasma and urine levels of NGAL rapidly and markedly increase. This major and early response (within few hours) is of particular interest to early detect and prevent AKI. In children scheduled for cardiac surgery, the AUC for NGAL at 2 and 4 h postbypass were 0.99 and 1.0, respectively.[29] In a study involving 88 general ICU patients, Constantin *et al.* showed that plasma NGAL increases 48 h before Risk, Injury, Failure, Loss, End-stage kidney disease criteria. In this study, a cutoff of 155 nmol/l

showed a sensitivity and specificity to predict AKI of 82 and 97%, respectively, with an AUC of 0.92 (95% CI, 0.85 to 0.97). These results were weakened by less conclusive findings in adult cardiac surgery, ICU, and emergency patients, in whom AUC for S-NGAL or U-NGAL varied from 0.54 to 0.79, which can be considered as moderately informative.[30–36] The main concern of NGAL interpretation in these large studies is that there is a wide overlap of NGAL values between AKI and non-AKI patients. Although a very low value (<200 nmol/l) is usually associated with no AKI, a higher value can be recorded both in AKI and non-AKI patients (false positive), especially in patients with a high
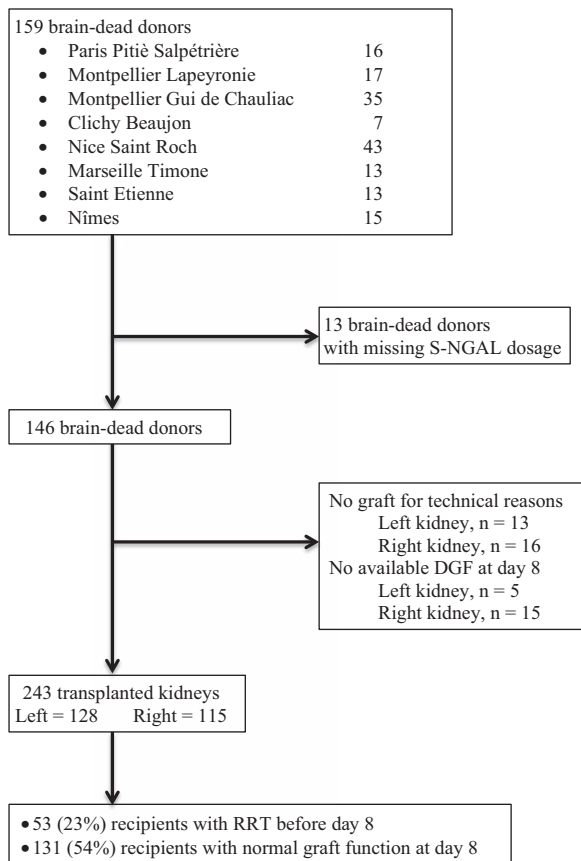
**Fig. 1.** Study flow chart. DGF = delayed graft function; RRT = renal replacement therapy; S-NGAL = serum neutrophil gelatinase-associated lipocalin.

systemic inflammatory response syndrome, which is usually observed during BD.[37] In the frame of renal transplantation, NGAL measurement after transplantation was suggested to be useful to follow transplanted patients and to predict graft recovery or failure.[20] Therefore, the usefulness of NGAL in the setting of kidney transplantation from BD donor is challenged. In the frame of BD donor, only one study tested the ability of NGAL to predict DGF.[22] In this study, neither S-NGAL nor U-NGAL in donor could accurately predict DGF in recipients. This previous study had several limitations: monocentric study, measurement of S-NGAL performed before the occurrence of BD in 36% of cases and systematic use of glucocorticoids. The design of the current study ruled out this methodological limitations and showed similar results.

Several hypotheses can be raised to explain our negative results concerning NGAL as biomarker predictive for DGF that markedly differ to other clinical situations in critically ill patients. First, we decided to perform NGAL measurement at the time of surgery to detect an occult renal dysfunction after the occurrence of BD and hemodynamic stabilization. However, Hollmen et al.[22] performed NGAL measurement earlier and they also failed to observe positive results. Thus, the timing does not appear as a valuable explanation for our

negative results. Second, it has been widely demonstrated that an aggressive management of BD donor increases the number and the quality of grafts.[6] Therefore, it can be hypothesized that a high quality of ICU care may limit AKI in BD donors. In our study, the median S-NGAL was very low: 108.5 ng/ml. Such low NGAL levels can be due to the efficacy of an aggressive donor resuscitation leading to a low proportion of significant AKI in our donors. Also, low levels of serum creatinine at the same time (table 1) confirm this hypothesis. It should also be noted that the S-NGAL values reported by Hollmen et al.[22] in a similar setting were also relatively low (median = 212 ng/ml). This reinforces the idea that AKI is nowadays well controlled by aggressive donor resuscitation. As the timing of S-NGAL measurement was performed earlier in the Hollmen et al.[22] study and because the median S-NGAL value was twice the value observed in the current study (212 *vs.* 108.5 ng/ml), it can be hypothesized that S-NGAL value decreases over time as a consequence of efficient donor management. It could also be hypothesized that serial measurement of NGAL (at admission and before surgery) could have been more informative, but the current result do not allow supporting this hypothesis. It could be interesting to test the ability of NGAL variations over time in donors to predict DGF in recipients. Third, the major factors leading to DGF might be postrecovery factors rather than factors related to pregraft donor conditions. In the current study, the multivariate analysis shows that cold ischemic time has the highest OR (tables 2 and 3), suggesting that postrecovery conditions are major determinant of graft function. Recently, Malinoski et al.[38] showed that age, cold ischemic time, and creatinine are independent factors of DGF. Finally, the weak prediction of DGF by S-NGAL observed in the current study may be related to the type of measurement itself. It could be argued that S-NGAL is less specific of renal damages than U-NGAL since U-NGAL detected in urine mainly derives from renal epithelial cells as a consequence of AKI.[39] However, in the study from Hollmen et al.,[22] U-NGAL was not superior to S-NGAL to predict DGF. S-NGAL can be produced through nonrenal (bone marrow, gut, and lungs) synthesis NGAL.[16] Another way of extra-renal NGAL production could be the systemic inflammatory response syndrome induced by BD, as NGAL is an acute phase protein, which depends on cytokine release.[16] As S-NGAL is filtered through the glomerulus, one cannot exclude that high U-NGAL concentration may also reflect extra-renal overproduction of NGAL. However, because we observed low values of NGAL in BD patients, the hypothesis that extra-renal S-NGAL production may interfere with its diagnostic accuracy is not likely.

The following limitations have to be considered to assess the clinical relevance of our results. First, in this multicenter trial, there was no recommended donor algorithm management, especially indications for RRT. Thus, we cannot exclude management heterogeneity between the different units leading to a less powerful interest of NGAL measurement. The
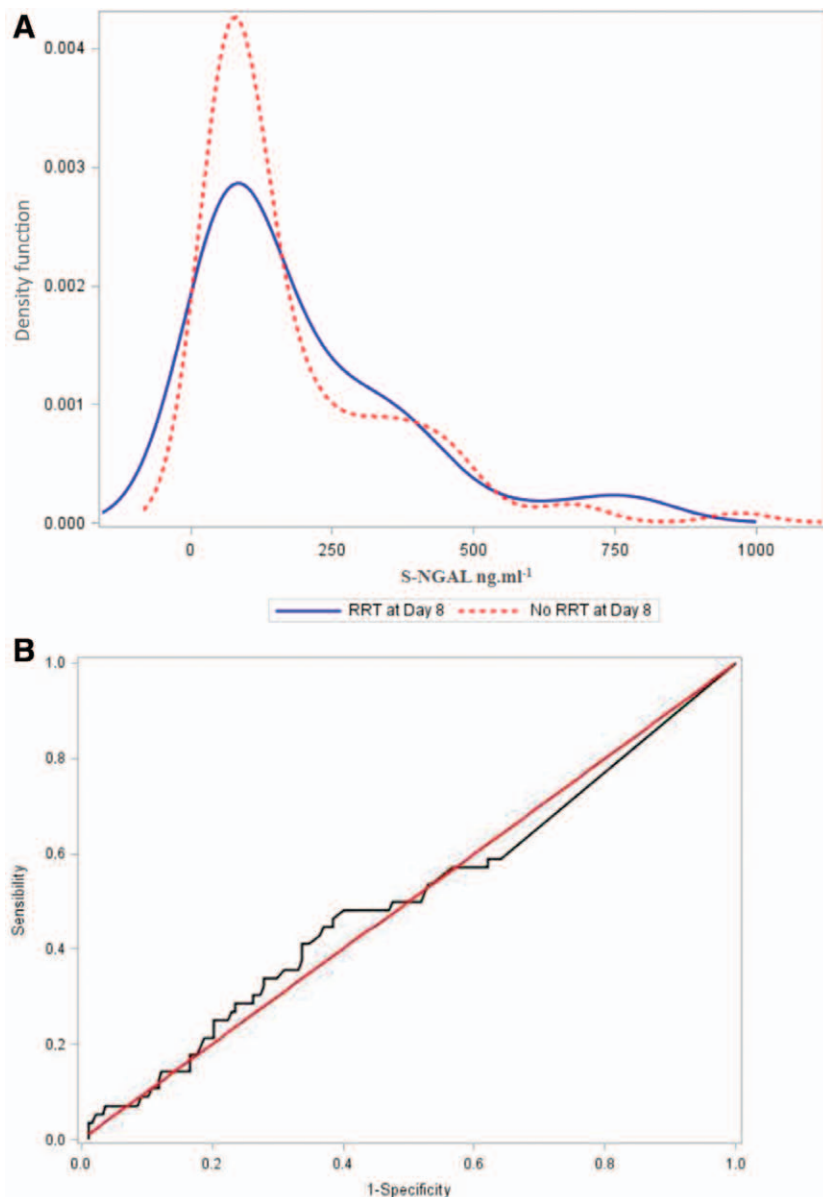
**Fig. 2.** (*A*) Distribution of serum neutrophil gelatinase-associated lipocalin (S-NGAL) values obtained from donors with no subsequent renal replacement therapy (RRT) in recipients at day 8 (*red dashed line*) and from donors with subsequent RRT in recipients at day 8 (*blue solid line*). The density function represents the number of patients with a given value of NGAL. (*B*) Receiver operator characteristic (ROC) curve for S-NGAL to predict the need for renal replacement therapy at day 8 postgraft. The area under the ROC curve was 0.50 (95% CI, 0.42 to 0.59). No cutoff value could be identified.

**Table 2.** Donors and Transplantation Factors that Influence the Requirement for Renal Replacement Therapy in Recipients in Uni- and Multivariate Logistic Mixed Model Analyses

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| Factor | OR (95% CI) | *P* Value | OR (95% CI) | *P* Value |
| NGAL increase >1 ng/ml | 1.001 (0.999–1.002) | 0.48 | 0.999 (0.997–1.002) | 0.57 |
| Cold ischemic time (per increase = 1 h) | 1.115 (1.057–1.177) | <0.001 | 1.116 (1.057–1.178) | <0.001 |
| Serum creatinine increase in donor >10 μmol/l | 1.064 (1.006–1.126) | 0.03 | 1.072 (1.004–1.145) | 0.04 |

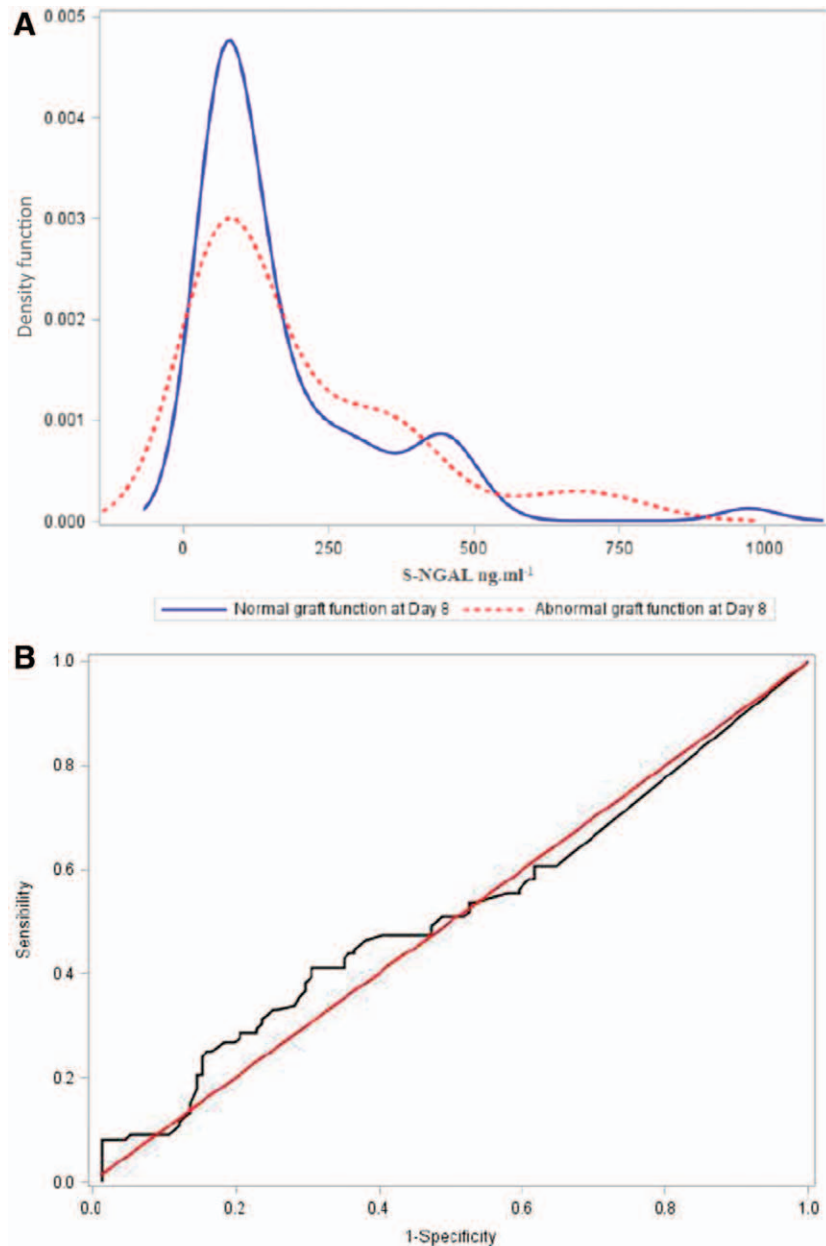NGAL = neutrophil gelatinase-associated lipocalin; OR = odds ratio.

**Fig. 3.** (*A*) Distribution of serum neutrophil gelatinase-associated lipocalin (S-NGAL) values obtained from donors with subsequent abnormal graft function in recipients at day 8 (*red dashed line*) and from donors with subsequent normal graft function in recipients at day 8 (*blue solid line*). The density function reflects the number of patients with a given value of S-NGAL. (*B*) Receiver operator characteristic (ROC) curve for S-NGAL to predict the failure to return to a normal renal graft function at day 8 postgraft. A normal graft function at day 8 was defined as urine output greater than 1,000 ml/day and creatinine less than 167 μmol/l during two consecutive days at day 8 posttransplantation.[12,25] The area under the ROC curve was 0.51 (95% CI, 0.44 to 0.59). No cutoff value could be identified.

current data show a trend for a center effect for slow graft function then we cannot reject the hypothesis that this study is underpowered to show a significant center effect. Second, we did not analyze recipient characteristics, especially age, warm ischemia time during transplantation, and severity scores. This lack of recipient's data theoretically limits the introduction of confounding variables in the model. Therefore, the current results need to be interpreted with caution.

Despite these limitations, DGF percentage is comparable to literature and usual predicting factors for DGF were also found. Then, the current population probably reflects a representative donor and recipient population. Moreover, because the NGAL values reported in the current study are very low (table 1), we think that the lack of link between NGAL and DGF is partly due to the lack of renal failure in donor and not because of confounding variables. Third, we did not analyze

**Table 3.** Donors and Transplantation Factors that Influence Failure to Return to a Normal Graft Function in Recipients in Uni- and Multivariate Logistic Mixed Model Analyses

| Factor | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | OR (95% CI) | P Value | OR (95% CI) | P Value |
| NGAL increase >1 ng/ml | 1.001 (0.999–1.003) | 0.26 | 1.000 (0.998–1.002) | 0.87 |
| Extended criteria donor | 1.573 (0.820–3.019) | 0.17 | 1.642 (0.848–3.180) | 0.14 |
| Cold ischemic time increase >1 h | 1.073 (1.022–1.127) | 0.005 | 1.073 (1.021–1.128) | 0.006 |
| Serum creatinine increase in donor >10 μmol/ml | 1.089 (1.021–1.161) | 0.01 | 1.091 (1.016–1.172 | 0.02 |

NGAL = neutrophil gelatinase-associated lipocalin; OR = odds ratio.

other relevant biomarker like cystatin C or cycle cell arrest biomarker or association of several markers that have recently been shown as promising.[40] Finally, It could be objected that only terminal creatinine value could have been studied, rather than creatinine variation. The current result suggests that creatinine variation over time is a better predictor than NGAL for DGF. This finding reinforces the use of scores as Risk, Injury, Failure, Loss, End-stage kidney disease or surrogates; those are mainly based on creatinine variation, and widely recommended in ICU patients. It has been demonstrated that donor terminal creatinine is strongly associated with DGF.[41,42] In the current study, we did not specifically studied final (terminal) creatinine value, but we recorded the variation of creatinine during the last 48 h of donor resuscitation. This variation was significantly associated with DGF. As we recorded creatinine value at the time of surgical procedure, this creatinine variation takes into account terminal creatinine value. Then, it can be postulated that the 10% creatinine variation reported in the current study indirectly reflect terminal creatinine value, but we did not specifically tested this hypothesis.

## Conclusion

Unlike what has been previously demonstrated in ICU and emergency patients, S-NGAL measurement in BD kidney donor at the time of surgery does not predict delayed or normal graft function after transplantation.

## Competing Interests

The authors declare no competing interests.

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## References

1. Shapiro R: End-stage renal disease in 2010: Innovative approaches to improve outcomes in transplantation. Nat Rev Nephrol 2011; 7:68–70

2. Page TF, Woodward RS: Cost-effectiveness of Medicare's coverage of immunosuppression medications for kidney transplant recipients. Expert Rev Pharmacoecon Outcomes Res 2009; 9:435–44

3. Ibrahim HN, Foley R, Tan L, Rogers T, Bailey RF, Guo H, Gross CR, Matas AJ: Long-term consequences of kidney donation. N Engl J Med 2009; 360:459–69

4. Cecka JM: Kidney transplantation in the United States. Clinical Transplants 2008; pp 1–18

5. Salim A, Martin M, Brown C, Rhee P, Demetriades D, Belzberg H: The effect of a protocol of aggressive donor management: Implications for the national organ donor shortage. J Trauma 2006; 61:429–33; discussion 433–5

6. Malinoski DJ, Patel MS, Daly MC, Oley-Graybill C, Salim A; UNOS Region 5 DMG Workgroup: The impact of meeting donor management goals on the number of organs transplanted per donor: Results from the United Network for Organ Sharing Region 5 prospective donor management goals study. Crit Care Med 2012; 40:2773–80

7. Hassanain M, Tchervenkov J, Cantarovich M, Metrakos P, Paraskevas S, Keith D, Baran D, Fernandez M, Mangel R, Chaudhury P: Delayed graft function has an equally bad impact on deceased donor renal graft survival in both standard criteria donors and expanded criteria donors. Transplant Proc 2009; 41:133–4

8. Hassanain M, Tchervenkov JI, Cantarovich M, Metrakos P, Paraskevas S, Keith D, Baran D, Fernandez M, Mangel R, Chaudhury P: Recovery of graft function early posttransplant determines long-term graft survival in deceased donor renal transplants. Transplant Proc 2009; 41:124–6

9. Sáinz MM, Toro JC, Poblete HB, Perez LF, Nicovani VH, Carrera MG: Incidence and factors associated with delayed graft function in renal transplantation at Carlos Van Buren Hospital, January 2000 to June 2008. Transplant Proc 2009; 41:2655–8

10. Quiroga I, McShane P, Koo DD, Gray D, Friend PJ, Fuggle S, Darby C: Major effects of delayed graft function and cold ischaemia time on renal allograft survival. Nephrol Dial Transplant 2006; 21:1689–96

11. Lebranchu Y, Halimi JM, Bock A, Chapman J, Dussol B, Fritsche L, Kliem V, Oppenheimer F, Pohanka E, Salvadori M, Soergel M, Tufveson G; MOST International Study Group: Delayed graft function: Risk factors, consequences and parameters affecting outcome-results from MOST, A Multinational Observational Study. Transplant Proc 2005; 37:345–7

12. Halloran PF, Hunsicker LG: Delayed graft function: State of the art, November 10–11, 2000. Summit meeting, Scottsdale, Arizona, USA. Am J Transplant 2001; 1:115–20

13. Salim A, Martin M, Brown C, Belzberg H, Rhee P, Demetriades D: Complications of brain death: Frequency and impact on organ retrieval. Am Surg 2006; 72:377–81

14. Saleh DA, Shebl FM, El-Kamary SS, Magder LS, Allam A, Abdel-Hamid M, Mikhail N, Hashem M, Sharaf S, Stoszek SK, Strickland GT: Incidence and risk factors for community-acquired hepatitis C infection from birth to 5 years of age in rural Egyptian children. Trans R Soc Trop Med Hyg 2010; 104:357–63

15. McIlroy DR, Wagener G, Lee HT: Biomarkers of acute kidney injury: An evolving domain. Anesthesiology 2010; 112:998–1004

16. Mishra J, Ma Q, Prada A, Mitsnefes M, Zahedi K, Yang J, Barasch J, Devarajan P: Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol 2003; 14:2534–43

17. Singbartl K, Kellum JA: AKI in the ICU: Definition, epidemiology, risk stratification, and outcomes. Kidney Int 2012; 81:819–25

18. Constantin JM, Futier E, Perbet S, Roszyk L, Lautrette A, Gillart T, Guerin R, Jabaudon M, Souweine B, Bazin JE, Sapin V: Plasma neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in adult critically ill patients: A prospective study. J Crit Care 2010; 25:176.e1–6

19. Malyszko J, Malyszko JS, Bachorzewska-Gajewska H, Poniatowski B, Dobrzycki S, Mysliwiec M: Neutrophil gelatinase-associated lipocalin is a new and sensitive marker of kidney function in chronic kidney disease patients and renal allograft recipients. Transplant Proc 2009; 41:158–61

20. Hollmen ME, Kyllönen LE, Inkinen KA, Lalla ML, Salmela KT: Urine neutrophil gelatinase-associated lipocalin is a marker of graft recovery after kidney transplantation. Kidney Int 2011; 79:89–98

21. Rostami Z, Nikpoor M, Einollahi B: Urinary neutrophil gelatinase associated lipocalin (NGAL) for early diagnosis of acute kidney injury in renal transplant recipients. Nephrourol Mon 2013; 5:745–52

22. Hollmen ME, Kyllönen LE, Inkinen KA, Lalla ML, Merenmies J, Salmela KT: Deceased donor neutrophil gelatinase-associated lipocalin and delayed graft function after kidney transplantation: A prospective study. Crit Care 2011; 15:R121

23. Wijdicks EF, Varelas PN, Gronseth GS, Greer DM; American Academy of Neurology: Evidence-based guideline update: Determining brain death in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2010; 74:1911–8

24. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996; 22:707–10

25. Perico N, Cattaneo D, Sayegh MH, Remuzzi G: Delayed graft function in kidney transplantation. Lancet 2004; 364:1814–27

26. Boutin C, Vachiéry-Lahaye F, Alonso S, Louart G, Bouju A, Lazarovici S, Perrigault PF, Capdevila X, Jaber S, Colson P,

Jonquet O, Ripart J, Lefrant JY, Muller L; pour le groupe AzuRéa: [Anaesthetic management of brain-dead for organ donation: Impact on delayed graft function after kidney transplantation]. Ann Fr Anesth Reanim 2012; 31:427–36

27. Ray P, Le Manach Y, Riou B, Houle TT: Statistical evaluation of a biomarker. Anesthesiology 2010; 112:1023–40

28. Vanmassenhove J, Vanholder R, Nagler E, Van Biesen W: Urinary and serum biomarkers for the diagnosis of acute kidney injury: An in-depth review of the literature. Nephrol Dial Transplant 2013; 28:254–73

29. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, Ruff SM, Zahedi K, Shao M, Bean J, Mori K, Barasch J, Devarajan P: Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 2005; 365:1231–8

30. Cruz DN, de Cal M, Garzotto F, Perazella MA, Lentini P, Corradi V, Piccinni P, Ronco C: Plasma neutrophil gelatinase-associated lipocalin is an early biomarker for acute kidney injury in an adult ICU population. Intensive Care Med 2010; 36:444–51

31. de Geus HR, Bakker J, Lesaffre EM, le Noble JL: Neutrophil gelatinase-associated lipocalin at ICU admission predicts for acute kidney injury in adult patients. Am J Respir Crit Care Med 2011; 183:907–14

32. Di Somma S, Magrini L, De Berardinis B, Marino R, Ferri E, Moscatelli P, Ballarino P, Carpinteri G, Noto P, Gliozzo B, Paladino L, Di Stasio E: Additive value of blood neutrophil gelatinase-associated lipocalin to clinical judgement in acute kidney injury diagnosis and mortality prediction in patients hospitalized from the emergency department. Crit Care 2013; 17:R29

33. Wagener G, Gubitosa G, Wang S, Borregaard N, Kim M, Lee HT: Urinary neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery. Am J Kidney Dis 2008; 52:425–33

34. Tuladhar SM, Püntmann VO, Soni M, Punjabi PP, Bogle RG: Rapid detection of acute kidney injury by plasma and urinary neutrophil gelatinase-associated lipocalin after cardiopulmonary bypass. J Cardiovasc Pharmacol 2009; 53:261–6

35. Koyner JL, Bennett MR, Worcester EM, Ma Q, Raman J, Jeevanandam V, Kasza KE, O'Connor MF, Konczal DJ, Trevino S, Devarajan P, Murray PT: Urinary cystatin C as an early biomarker of acute kidney injury following adult cardiothoracic surgery. Kidney Int 2008; 74:1059–69

36. Haase-Fielitz A, Bellomo R, Devarajan P, Story D, Matalanis G, Dragun D, Haase M: Novel and conventional serum biomarkers predicting acute kidney injury in adult cardiac surgery—A prospective cohort study. Crit Care Med 2009; 37:553–60

37. Murugan R, Venkataraman R, Wahed AS, Elder M, Carter M, Madden NJ, Kellum JA; HIDonOR Study Investigators: Preload responsiveness is associated with increased interleukin-6 and lower organ yield from brain-dead donors. Crit Care Med 2009; 37:2387–93

38. Malinoski DJ, Patel MS, Ahmed O, Daly MC, Mooney S, Graybill CO, Foster CE, Salim A; United Network for Organ Sharing (UNOS) Region 5 Donor Management Goals (DMG) Workgroup: The impact of meeting donor management goals on the development of delayed graft function in kidney transplant recipients. Am J Transplant 2013; 13:993–1000

39. Yang J, Mori K, Li JY, Barasch J: Iron, lipocalin, and kidney epithelia. Am J Physiol Renal Physiol 2003; 285:F9–18

40. Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, Bihorac A, Birkhahn R, Cely CM, Chawla LS, Davison DL, Feldkamp T, Forni LG, Gong MN, Gunnerson KJ, Haase M, Hackett J, Honore PM, Hoste EA, Joannes-Boyau O, Joannidis M, Kim P, Koyner JL, Laskowitz DT, Lissauer ME, Marx G, McCullough PA, Mullaney S, Ostermann M, Rimmelé T, Shapiro NI, Shaw AD, Shi J, Sprague AM, Vincent JL, Vinsonneau C, Wagner L, Walker MG, Wilkerson RG,

Zacharowski K, Kellum JA: Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care 2013; 17:R25

41. Moore J, Tan K, Cockwell P, Krishnan H, McPake D, Ready A, Mellor S, Hamsho A, Ball S, Lipkin G, Borrows R: Predicting early renal allograft function using clinical variables. Nephrol Dial Transplant 2007; 22:2669–77

42. Irish WD, Ilsley JN, Schnitzler MA, Feng S, Brennan DC: A risk prediction model for delayed graft function in the current era of deceased donor renal transplantation. Am J Transplant 2010; 10:2279–86

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