Identifying Biomarkers of Delayed Graft Function in Kidney Transplant Patients

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BACKGROUND

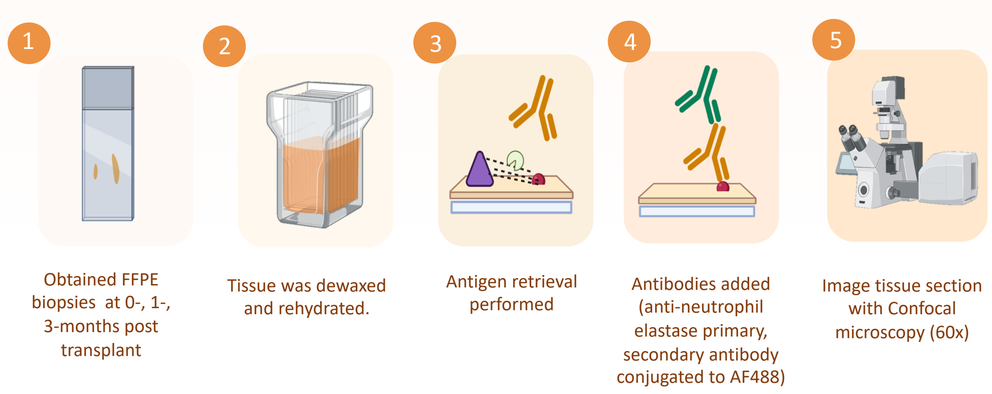
End stage renal disease (ESRD) is a substantial disease burden for both the patient and the economy – accounting for approximately $1 billion of the annual Australian healthcare expenditure.[1] Kidney transplantation is the preferred treatment for ESRD because it offers better survival advantage but can be complicated by acute kidney injury in the allograft, manifested as delayed graft function (DGF) early post-transplantation. DGF is most commonly defined by the need for dialysis within the first post-operative week and is associated with overall poorer graft and patient outcomes.

HYPOTHESIS & AIMS

Our lab previously identified an upregulation in neutrophil gene signal in DGF kidney biopsy samples and so we hypothesize that neutrophils can be detected as an early biomarker of DGF in kidney allografts. Hence, our aim is to investigate the role of neutrophils in the development of allograft acute kidney injury and DGF and to further interrogate relevant clinical data to identify important influences on outcomes following the development of DGF.

METHODS & RESULTS

Neutrophils are not a specific biomarker for DGF



Stains for neutrophil were performed on bio-banked kidney biopsy tissue (preserved in FFPE blocks collected as part of routine clinical care) of patients enrolled in the Australian Chronic Allograft Dysfunction study, Westmead Hospital. Clinical data was also collected on this cohort.

Neutrophils were identified by co-localisation of neutrophil elastase with the nucleus and counted by two blinded, independent observers. Neutrophil count was not different between patients who did or did not develop DGF (Fig 1).

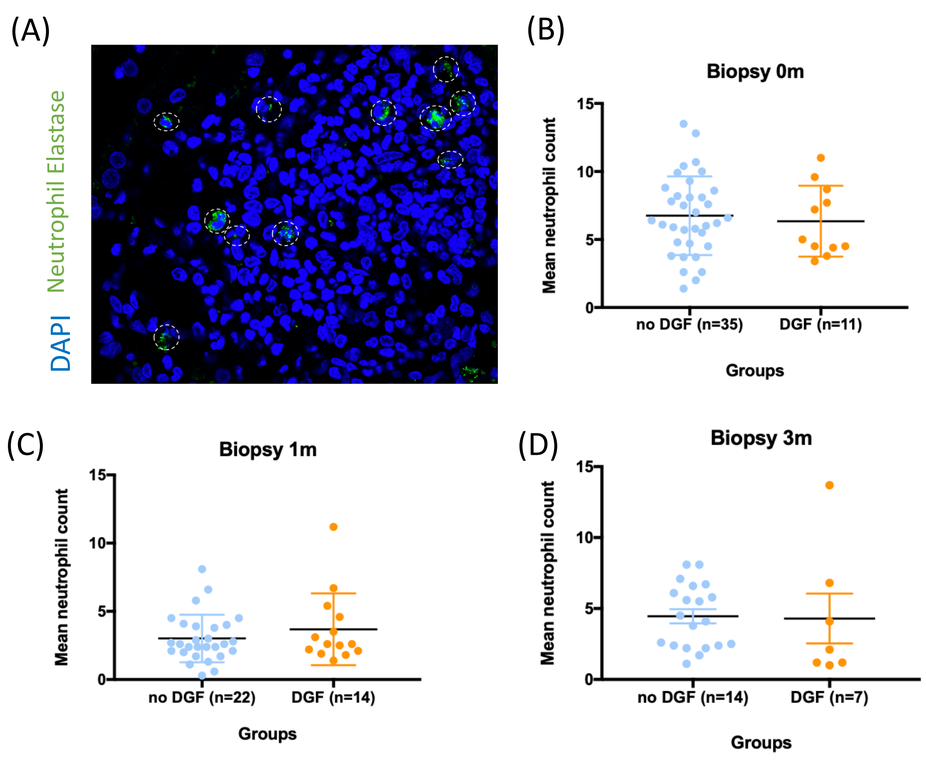
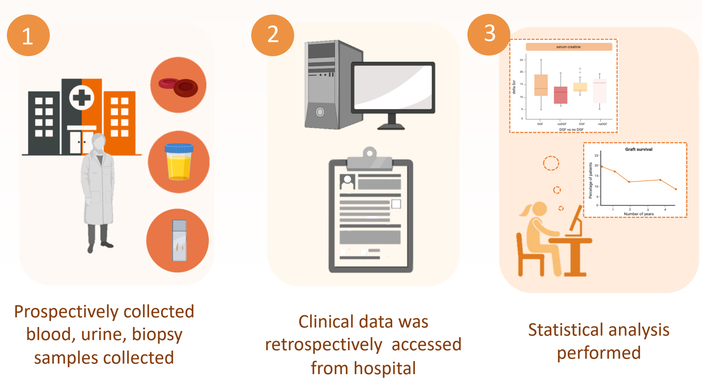


Figure 1. (A) Immunofluorescence of neutrophil elastase using patient biopsy samples. Neutrophils were counted by colocalisation to the nucleus per high power field. (B) Mean (±SD) neutrophil count for 0-month, (C) 1-month and (D) 3-month biopsy samples for DGF vs no DGF. Groups were compared using Mann-U-Whitney test.

DGF - Relevant Clinical Risk Factors and Outcomes



The median age of the cohort was 47 years old (n=171)

- DGF occurred in 20% of the cohort following kidney or kidney-pancreas transplantation (n=35).
- DGF was more likely to occur following cadaveric transplantation (p=0.001) and donation after cardiac death (p=0.01).
- Biopsy proven acute rejection was higher in DGF patients (32% for DGF vs 13% for no DGF; p=0.01) but did not impact 12 month renal function (Fig 2), or the overall patient or allograft survival compared to those who did not develop DGF. (Fig 3).

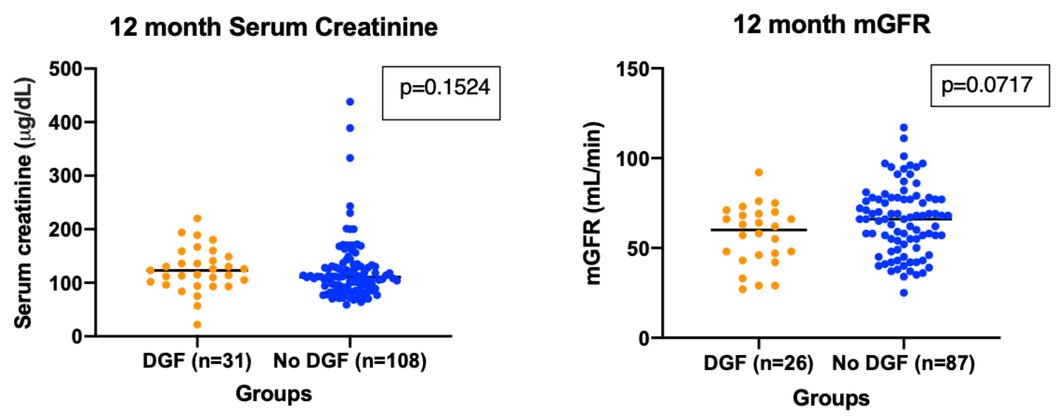


Figure 2. Comparison of post transplant graft function using surrogate markers serum creatinine and measured glomerular filtration rate (mGFR), analysed with Mann-U-Whitney t test.

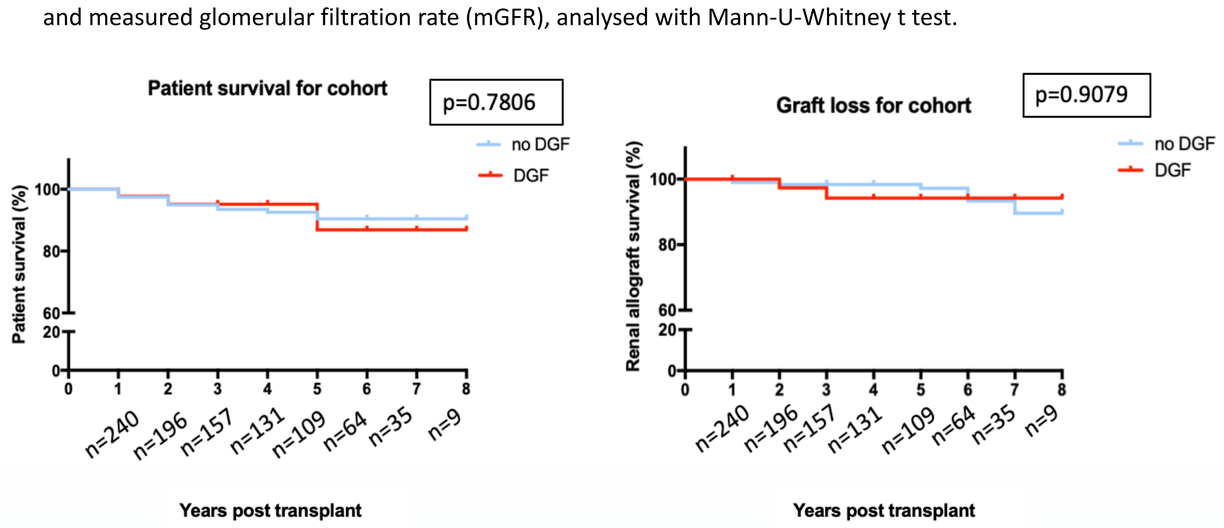


Figure 3. Comparison of patient and graft survival between DGF (n=35) versus no DGF groups (n=111) using Kaplan Meier curve and Log-Rank test.

Conclusions & Future Directions

We have identified several factors that are associated with the diagnosis of delayed graft function (DGF). These include cadaveric donor transplantation, grafts donated after cardiac death. Biopsy proven acute rejection rates was higher in DGF patients, leading to extra immunosuppression burden. We are currently collecting more patient data and will continue analysis to report clinical findings, which may guide future development of therapy strategies.

References:

1. Cass A et al. The Economic Impact of End Stage Kidney Disease in Australia: projects to 2020. Published 2010. Available at: http://www.kidney.org.au/LinkClick.aspx?fileticket=vave4WFH73U