Chronic kidney disease post-liver transplantation

Aisling O’Riordan¹, Vincent Wong¹, P. Aiden McCormick², John E. Hegarty² and Alan J. Watson¹

1Department of Nephrology and 2National Liver Transplant Unit, St Vincent’s University Hospital, Elm Park, Dublin 4, Ireland

Abstract

Background. Renal disease is a recognized complication of orthotopic liver transplantation (OLT). We aimed to determine the incidence of all stages of chronic kidney disease (CKD), as defined in the Kidney Disease Outcomes Quality Initiative Guidelines. We also wanted to determine the risk factors for development of CKD and its impact on patient survival.

Methods. All patients who underwent cadaveric OLT, from January 1993 until July 2004, were analysed. The glomerular filtration rate (GFR) was determined using the equation developed by the Modification of Diet in Renal Disease Study. Thirty potential risk factors were examined by univariate and multivariate ordinal logistic regression analysis. Kaplan–Meier survival analysis, the log-rank test and Cox regression analysis were performed to evaluate the survival data.

Results. A total of 230 patients were included (107 males and 123 females) with a mean age of 47.7 years (4.5–70.35). Mean follow-up was 5.57 years (0.53–16.5). The following was the 10 year cumulative incidence for each stage of CKD: 0/1, 9.61%; 2, 53.71%; 3, 56.77%; 4, 6.11%; 5, 2.62%. Female gender, age, pre-OLT proteinuria, lower GFR from 1 year and higher creatinine from 6 months were associated with progression of CKD. The use of tacrolimus had a favourable impact. A GFR < 30 ml/min, the need for re-transplantation and fulminant hepatic failure were all associated with reduced patient survival.

Conclusions. Moderate CKD was very prevalent. We identified the risk factors for progression of CKD and also that severe CKD was associated with reduced patient survival.

Keywords: calcineurin inhibitor; chronic kidney disease; end-stage renal disease; glomerular filtration rate; liver transplantation; survival

Introduction

Chronic kidney disease (CKD) is a recognized complication of orthotopic liver transplantation (OLT). Several potential causes exist including hepatitis C virus (HCV)-related renal disease, hypertension, diabetes mellitus and other glomerular diseases such as IgA nephropathy [1–4]. There is, therefore, a broad differential diagnosis for CKD and, while other causes must be considered, it is felt by several authors that the use of calcineurin inhibitors (CI) is a major contributor [5–7]. Since the introduction of the first of these immunosuppressive agents in the 1980s, the survival outcomes for transplant recipients have been revolutionized [8,9] but they have had an adverse impact on renal function. Long-term use of CIs, namely cyclosporine A (CYA) and tacrolimus can result in nephrotoxicity, the pathogenesis of which is thought to be due to reduced renal blood flow and interstitial fibrosis [10,11].

It has been shown that up to 18% of the patients can develop a glomerular filtration rate (GFR) of < 29 ml per min per 1.732 of body surface area (ml/min) by 5 years post-transplantation [5], however, rates vary depending on the definitions used. Some investigators have used the classification outlined in the Kidney Disease Outcomes Quality Initiative (K/DOQI) Guidelines and others have used specific creatinine levels to stratify patients [12–14] making interpretation and comparison of results difficult.

It is important to diagnose and treat CKD appropriately because of the documented link with increased morbidity and mortality. Ojo et al. [5] revealed that recipients of non-renal solid organ transplants with CKD had a mortality risk of 4.55 compared with their counterparts who had normal renal function.

To date, most studies have focused on the development of severe or end-stage renal disease (ESRD) but few have looked at the full spectrum of CKD. Renal impairment may be reversible if diagnosed early, so it needs to be identified and treated promptly. We therefore need to gain a better understanding of the prevalence of all stages of CKD and also what factors influence progression to ESRD.
The aims of this study were to determine:

(i) The incidence of all stages of CKD post-OLT.
(ii) The risk factors associated with progression from mild CKD to ESRD.
(iii) The impact of CKD on patient survival.

Subjects and methods

Patient population

The medical records, radiology and laboratory results of all patients (n = 300) who underwent cadaveric OLT in the Irish National Liver Transplant Unit from the inception of the programme in January 1993, until the cut-off date of July 2004, were retrospectively analysed. A number of patients (n = 38) who were initially transplanted in the UK, but were subsequently transferred back to Ireland for their long-term follow-up, were also included. This subset of patients was not included in the survival analysis. Only first transplants surviving beyond 6 months post-OLT and those, whose records contained sufficient information, were included (n = 230).

Definitions

CKD was divided into stages as defined by the K/DOQI Clinical Practice Guidelines [12]. Patients were classified according to the following criteria using their most recent stable GFR: stage 5 (ESRD, dialysis or a GFR <15 ml/min), stage 4 (GFR 15–29 ml/min), stage 3 (GFR 30–59 ml/min), stage 2 (kidney damage with a GFR of 60–89 ml/min) and stage 1 (kidney damage with a GFR >90 ml/min). Normal renal function was designated as stage 0.

Kidney damage can be diagnosed by either:

(i) abnormal renal pathological, laboratory or radiological markers for >3 months, with or without a decreased GFR; or
(ii) a GFR <60 ml/min for >3 months.

Variables

Several parameters were examined for an association with CKD. The pre-OLT variables evaluated included; age at the time of transplantation, gender, diabetes mellitus (fasting blood glucose >7 mmol/l or random blood glucose >11.1 mmol/l[15]), hypertension (systolic and diastolic blood pressure >140 and 90 mmHg, respectively [16]), HCV infection, cytomegalovirus (CMV) donor/recipient status, period of transplantation (1993–98 vs 1999–2004), serum creatinine (µmol/l), 24-hour total urinary protein (g/l) and any dialysis requirements. The Mayo End-Stage Liver Disease (MELD) scores were calculated for each patient using the following equation: 9.6 × log2 [creatinine (µmol/l) / 88.4] + 3.8 × log2 [bilirubin (µmol/l) / 17.1] + 11.2 × log2 (international normalised ratio) + 6.43 [17].

The common indications for OLT such as alcoholic liver disease (ALD), viral hepatitis (VH), fulminant hepatic failure (FHF), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), autoimmune chronic active hepatitis (AICAH), cryptogenic cirrhosis (CC) and hepatoma were also evaluated for an association with development of CKD.

The immunosuppression regimen was recorded, as were the initial and most recent trough serum CI levels (ng/ml). These levels were calculated from the mean of the measurements in the initial 2 weeks post-OLT and again from the mean of the three most recent levels. Post-OLT complications such as de novo diabetes mellitus, and hypertension, as well as the need for re-transplantation were noted. The following post-OLT renal parameters were evaluated: a history of acute renal failure (ARF), defined as a 3-fold increase in the post-OLT creatinine from baseline or the need for dialysis or a history of acute renal injury (ARI), defined as a doubling of the post-OLT creatinine from baseline [18]. The serum creatinine at the following intervals: 1, 3 and 6 months and at 1, 5 and 10 years post-OLT, along with the GFR at 1, 5 and 10 years were determined. Each patient’s most recent weight (kg) was also recorded. The GFR was calculated using the equation developed by the Modification of Diet in Renal Disease (MDRD) Study group using each patient’s stable creatinine at the stated time intervals [19]:

\[
\text{GFR} = \frac{175}{\text{creatinine (µmol/l)}} \times 0.011 \times \text{age}^{0.176} \times \text{urea (mmol/l)}^{1.209} \times \text{albumin (g/l)}^{0.168} \times (1.180, \text{if black}) \times (0.762, \text{if female})
\]

Using this information, the 10 year cumulative incidence of each stage of CKD was determined along with the point prevalence at 1, 5 and 10 years and overall (using each patient’s last GFR). Finally, the influence of various factors on overall patient survival post-OLT were evaluated; stage of CKD, age, gender, diabetes mellitus, ARI and ARF, need for re-transplantation, interval creatinine measurements, FHF, HCV, HBV and period of transplantation.

Statistical analysis

An ordinal model of CKD was used and univariate ordinal logistic regression analysis was performed to evaluate the relationship between the stated variables and progression towards ESRD. Multivariate analysis was then performed on variables that were found to be significant (P < 0.05) in the univariate models. Kaplan–Meier survival analysis was used to calculate the cumulative incidence and the log-rank test was used to compare the strata. Both of these methods of statistical analysis, along with Cox regression analysis were performed to evaluate the survival data. SPSS 11.0.1 (SAS, Chicago, IL, USA) and JMP 5.0 (SAS Institute Inc., Cary, NC, USA) statistical packages were used to perform the analysis and a P-value <0.05 was considered significant. Percentages with the corresponding number of patients (n), mean ± SD (minimum–maximum), odds ratios (OR), hazard ratios (HR) and their 95% confidence intervals (95% CI) are reported.

Results

Patient population

A total of 300 patients received 359 OLTs within the specified time period, out of which, 230 patients met the inclusion criteria for analysis. Thirty-eight of the patients were transplanted in centres throughout the UK but received their long-term follow-up in Ireland. Insufficient information was available to accurately stratify patients into stage 1 as not all patients with a
GFR >90 ml/min had information available to exclude kidney damage. Therefore, all the patients with a GFR >90 ml/min were categorized as stage 0/1. Mean follow-up from the time of transplantation was 5.57 ± 3.99 years (0.53–16.49). Twenty (8.69%) patients required re-transplantation during the course of follow-up. There were 107 (46.52%) males and 123 (53.47%) females included in the study. The mean age was 47.67 ± 13.25 years (4.50–70.35). The mean GFR ± SD for each of the stages was as follows: stage 5, 10.32 ± 3.69; stage 4, 25.26 ± 3.92; stage 3, 47.81 ± 7.34; stage 2, 71.16 ± 8.16 and stage 0/1, 103.55 ± 13.50 (P = 0.0001).

Incidence of renal disease

The point prevalence for each stage of CKD based on each patient’s last stable GFR was: stage 5, 0.87% (n = 2); stage 4, 3.91% (n = 9); stage 3, 41.30% (n = 95); stage 2, 44.78% (n = 103) and stage 0/1, 9.13% (n = 21). Estimation of the prevalence of the various CKD stages at 1 and 5 years revealed that the vast majority of patients surviving to 1 year post-OLT (94.32%; n = 200) had an abnormal GFR and, in those surviving to 5 years post-OLT, the majority (71.11%; n = 73) had a GFR <60 ml/min.

In addition to the point prevalence figures, 10 year cumulative incidences were also calculated. Some patients progressed from one stage to another over the course of 10 years, hence are included in more than one stage. A total of 6.52% (n = 15) had a GFR <30 ml/min and the 10 year cumulative incidences for all the individual stages of CKD are illustrated in Figure 1.

Clinical features pre-OLT

Increasing age (P < 0.000000001; OR, 1.08; 95% CI: 1.05–1.11), female gender (P = 0.01; OR, 1.90; 95% CI: 1.15–3.14), an OLT from a CMV positive donor to a positive recipient (P = 0.02; OR, 2.96; 95% CI: 1.16–7.55) and pre-OLT diabetes mellitus (P = 0.05; OR, 2.27; 95% CI: 1.01–5.12) were associated with increased risk of progression to ESRD, by univariate analysis. The other pre-OLT variables were not significantly associated. Further information on pre-OLT diabetes mellitus and hypertension is included in Table 1. Only 47% (n = 108) of patients were evaluated for proteinuria pre-OLT (by a 24-hour urine collection), however, we found that 40.18% (n = 45) of those had levels of >0.15 g/l. The mean level was 0.21 ± 0.29 g/l (0.00–2.09), which was also significantly associated with the progression of renal disease (P = 0.01; OR, 5.36; 95% CI: 1.41–20.45).

Indications for OLT

The most common single indications for OLT were PBC (20.86%), ALD (13.47%) and PSC (12.61%) and the overall results are outlined in Figure 2. PBC (P < 0.001; OR, 3.02; 95% CI: 1.59–5.74) was significantly associated with progression to ESRD, by univariate analysis, but none of the other indications for OLT were found to be significant.

Renal transplantation and renal biopsy results

Six patients (four males and two females) in the cohort underwent renal transplantation during the follow-up. Having a renal transplant did not influence progression of CKD (P = 0.78; OR, 2.181; 95% CI: 0.27–5.75). Four received simultaneous liver and kidney transplants at the time of their first OLT. All underwent renal biopsies, the results of which included amyloidosis, chronic glomerulonephritis, cyclosporine nephrotoxicity, diabetic nephropathy, anti-glomerular basement membrane disease and focal and segmental glomerulosclerosis. The mean follow-up was 7.29 ± 3.58 years (2.91–11.67). Three of the four patients who underwent simultaneous liver and kidney transplantation developed stage 3 CKD. The fourth patient developed stage 2 CKD. The final two patients were maintained on haemodialysis for 6 and 18 months, respectively, after their first OLT and subsequently received a renal transplant. These two patients now have stages 2 and 3 CKD, respectively.

Table 1. Diabetes and hypertension pre- and post-OLT

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
<th>P</th>
<th>OR</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pre-OLT</td>
<td>25</td>
<td>10.87%</td>
<td>0.05</td>
<td>2.27</td>
<td>1.01–5.12</td>
</tr>
<tr>
<td>De novo</td>
<td>57</td>
<td>13.91%</td>
<td>NS</td>
<td>NS</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-OLT</td>
<td>15</td>
<td>6.52%</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>De novo</td>
<td>122</td>
<td>46.52%</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

OLT, orthotopic liver transplantation; n, number of patients; %, frequency; NS, not significant; OR, odds ratio; CI, confidence interval.
Post-OLT variables

All of the post-OLT factors outlined above were examined for an association with the development of ESRD. Only an increasing serum creatinine from 6 months onwards ($P = 0.02$; OR, 1.01; 95% CI: 1.00–1.02) was found to be associated with the progression of CKD by univariate analysis. An increasing calculated GFR from 1 year onwards ($P < 0.0000000000005$; OR, 0.92; 95% CI: 0.90–0.94) predicted a reduced risk of progression. Neither diabetes nor hypertension, were significantly associated, but there was an increase in the prevalence of both conditions post-OLT (Table 1).

Immunosuppression

The principle CI used was CYA in 26.95% ($n = 62$) of patients and a further 52.17% ($n = 120$) were treated with tacrolimus. Both drugs were used sequentially in 20.43% ($n = 47$) of the patients. Only 0.43% ($n = 1$) of the patients had never been treated with a CI. Triple therapy with either mycophenolate mofetil or azathioprine, (in combination with low dose steroids and a CI) was used in 91.30% ($n = 210$) of the patients. The remainder were treated with dual therapy comprising either a CI and steroids or a CI and an anti-metabolite. Based on each patient’s most recent immunosuppression regimen, 45.65% ($n = 104$) were treated with azathioprine, 27.83% ($n = 64$) with mycophenolate mofetil and 28.26% ($n = 65$) with steroids. Two patients (0.87%) had sirolimus added to a CI for chronic rejection. Induction agents were not used. By univariate analysis, patients who progressed towards ESRD had lower tacrolimus levels, perhaps reflecting a lower tacrolimus dose ($P = 0.02$; OR, 0.26; 95% CI: 0.08–2.30 when levels >15 ng/ml were compared with those <5 ng/ml). CYA levels did not have an impact on CKD stage. Use of tacrolimus was associated with a lower risk of developing CKD ($P = 0.02$; OR, 0.54; 95% CI: 0.33–0.89).

Multivariate analysis

Multivariate ordinal logistic regression analysis was performed using all factors that were found to be significant by univariate analysis and the results are displayed in Table 2. A higher serum creatinine from 6 months and a decreasing GFR from 1 year onwards were significantly associated with development of ESRD as was increasing levels of pre-OLT proteinuria, increasing age and female gender. The use of tacrolimus reduced the risk of progression, however, the use of CYA was not significant.

Patient survival

Univariate Kaplan–Meier analysis was performed to analyse which factors reduced the overall patient survival and the following parameters were found to be significantly associated: GFR <30 ml/min, ARF and ARF post-OLT, the need for re-transplantation and FHF. The Kaplan–Meier curves comparing patients with a GFR above and below 30 ml/min are displayed in Figure 3. Having milder stages of CKD did not influence patient survival. Factors that were significant ($P < 0.05$), by univariate survival analysis, were entered into a multivariate Cox regression analysis model and the independently significant predictors of the overall patient survival are displayed in Table 3.

Discussion

As liver transplant recipient survival increases, so too will the incidence of renal disease. Several studies have evaluated the incidence of severe CKD and ESRD post-OLT, but there is less of an understanding of the extent and implications of the milder stages of CKD.
patients in one cohort have a creatinine >176.8 μmol/l (2 mg/dl) after a median follow-up of 5 years [24]. It is also important to note the large percentage of patients in our study who had stages 2 and 3 CKD. There was a cumulative incidence of only 9.61% of patients who had a normal GFR >90 ml/min at 10 years. This could have serious implications in terms of long-term renal function because, as graft and patient survival improve, the number of individuals progressing to ESRD would also increase. Indeed, it is known that the annual incidence of developing a creatinine of >250 μmol/l is 0.8% [13].

It is essential, in terms of preventative and therapeutic strategies, that patients susceptible to renal disease are identified and risk factors recognized. The most consistently identified associated variables are those of elevated post-OLT creatinine levels and increasing age [5,6,13,14,20,22,23]. Using similar definitions of CKD to those used in this study, abnormal renal function as early as pre-OLT and ARF post-OLT is shown to be prognostic by some authors [5,14]. We identified an association between an abnormal GFR at 1 year and the later development of severe CKD correlating with the findings of Cohen et al. [25], who demonstrate that a lower GFR at 1 year identifies patients at risk of chronic renal dysfunction. Female gender is also recognized as a risk factor for renal disease post-OLT [5]. It is typically the male gender that is associated with the progression of renal disease in the general population, but the reason for this inconsistency is unclear [26]. It is of no surprise that proteinuria is associated with CKD as it is known to be a significant predictor in both the general and liver transplant populations [27,28]. We would have also liked to examine this association at intervals post-OLT but, unfortunately, this test was not routinely performed unless the patients had evidence of a reduced GFR. We would suggest that, given the strong association with progression to ESRD, this investigation should be performed more routinely. Finally, we also found a beneficial effect of tacrolimus use, compared with CYA, which retarded the progression to ESRD. This has been previously noted [5,29,30], there is conflicting evidence in the literature, as many investigators do not identify any potential risk factors by other authors include diabetes, CMV, CYA levels, race, HCV and the need for re-transplantation [5,13,23].

Identification of the risk factors for development of ESRD is crucial as not only does renal dysfunction have implications in terms of an increased demand on resources but also, it is significantly associated with a higher patient mortality rate [5,33]. We found that those with a GFR <30 ml/min had poorer overall

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**Table 3. Cox regression analysis of overall patient survival**

<table>
<thead>
<tr>
<th>GFR</th>
<th>HR (95%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 ml/min</td>
<td>3.05</td>
<td>0.02</td>
</tr>
<tr>
<td>Re-transplantation</td>
<td>2.05</td>
<td>0.001</td>
</tr>
<tr>
<td>Fulminant hepatic failure</td>
<td>5.78</td>
<td>0.01</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; GFR, glomerular filtration rate measured in millilitres per minute per 1.732 of body surface area.

The majority of the researchers use a specific serum creatinine threshold to define CKD [6,13,20]. This is not the optimal method for stratifying patients as the serum creatinine can vary depending on an individual’s gender, weight and nutritional status. Instead, it is widely recommended that one of the commonly used equations be used to estimate the GFR. In 2002, the K/DOQI Guidelines defined the stages of CKD based on GFR. The commonly used formulas (Cockcroft–Gault or MDRD) may not be as valid in patients with liver disease as they were originally developed for patients with renal disease. They are not as precise when used in liver transplant recipients, perhaps due to the reduced muscle mass of this patient population, however, the MDRD equation has been found to be the most accurate [21]. Therefore, we used the MDRD equation to calculate GFR and then stratified patients according to the K/DOQI Guidelines. This approach is also taken by Ojo et al. [5] in his study evaluating stages 4 and 5 CKD using the MDRD equation.

We found that the 10 year cumulative incidence of patients with a GFR <30 ml/min was 6.52%. Other authors report similar results but it is difficult to compare rates from different studies due to the diversity of definitions in use [22,23]. Up to 28% of
survival with a hazard ratio of 3.05. Similarly, Gonwa et al. [34] demonstrate this link, finding that at 13 years post-OLT, survival of patients with ESRD is only 28.2% compared with 54.6% in those with preserved renal function. With Cox regression analysis, we also found that not only did renal function influence the survival, but so too did an initial presentation with FHF and the need for re-transplantation during follow-up, as these patients would generally be more unwell.

In this cohort, 2.61% (n = 6) of the patients underwent renal biopsy (the individual results are outlined above), all of them having developed ESRD and eventually needing to undergo renal transplantation. Other studies evaluating biopsy findings in similar cohorts of patients show a wide variety of pathological lesions in the liver transplant population including diabetic nephropathy, focal and segmental glomerulosclerosis, IgA and membranous glomerulonephritis. We too found a number of different aetiologies, hence, although the predominant finding in the literature is pathology relating to CI use (such as thrombotic microangiopathy, vasculopathy, tubular atrophy and glomerular sclerosis) [7,13,35,36], it is very important that other causes be considered and treated appropriately.

This study does have a number of limitations. As it was retrospective, we were unable to obtain conclusive data on issues such as the definitive diagnosis for each case of pre-OLT renal impairment or post-OLT ARF and ARI. We would also have liked to evaluate other known CKD risk factors such as obesity, smoking and dyslipidaemia, but retrospective data was not readily available on these areas. We also included six OLT recipients who had also undergone renal transplantation. It could be argued that they should have been excluded as they differ from the rest of the subjects given the potential immunological reasons for renal impairment. However, renal transplantation had no association with the progression of CKD in this cohort, so they were included.

We have outlined that there was a strong evidence that it was possible to recognize OLT recipients susceptible to CKD at an early stage. Strategies need to be put in place for the early detection of these individuals and then preventative measures introduced to retard the progression of CKD. In many cases, it may not be possible to reverse CKD but it may be possible to slow deterioration to ESRD. Approaches should include initial identification of patients by routine screening for albuminuria and measurement of GFR followed by an early referral to a nephrology service. Hypertension needs to be rigorously controlled with a target blood pressure of 130/80mmHg for patients with non-diabetic kidney disease and both angiotensin-convertng enzyme (ACE) inhibitors and angiotensin receptor blockers are the preferred anti-hypertensive agents in those who also have evidence of proteinuria [37].

The use of nephrotoxic agents should be minimized with CI levels being kept within therapeutic targets. If CKD progresses, then alternative immunosuppressive regimens may need to be considered where non-nephrotoxic agents such as sirolimus and mycophenolate mofetil are used either instead of or in combination with low dose CIs [38–40]. Sirolimus has been used alone or in combination with steroids and mycophenolate mofetil with an improvement in renal function and without a significant increase in rejection rates [38,39]. Similarly, mycophenolate mofetil is a useful alternative in patients with CI nephrotoxicity, however, there may be a risk of increased transplant rejection rates with mycophenolate mofetil monotherapy [40,41].

In conclusion, we evaluated the risk factors for progression from mild renal disease to ESRD and also, the cumulative incidence of all stages of CKD in a liver transplant population. Particularly notable was the large percentage of the cohort who had moderate renal disease. We also outlined the significant implications CKD has in terms of reduced patient survival. A targeted approach is required for the early identification and treatment of affected individuals to prevent progression to ESRD.

Acknowledgements. This work is sponsored by a Newman scholarship from Baxter Healthcare Ltd. (Dublin, Ireland) and also by a research bursary from Amgen (Dublin, Ireland) and the Irish Nephrological Society.

Conflict of interest statement. None declared.

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