INTRODUCTION

End-stage liver disease is frequently associated with various forms of severe kidney damage. The clinical impact and pathogenesis has been widely studied, especially in patients with ascites, pathological electrolyte balance and hepatorenal syndrome. However, most children and young persons with chronic liver disease (CLD) do not develop liver failure, not even with a potentially lethal CLD. Our aim was to investigate the impact of renal damage in a typical clientele of a tertiary referral centre in paediatric hepatology, representing the whole spectrum of the disease burden, including both progressive and non-progressive forms of CLD. Recently, we...
have reported data on renal function in a relatively large group of children with CLD at the time of referral. This means that the data were collected before any treatment had started for the liver disease. Our study showed surprisingly well-preserved renal function or even hyperfiltration in certain diagnostic groups. We have also found that this hyperfiltration could be documented by measured but not by estimated GFR. Since the diagnostic spectrum of our patients with CLD reflected the clinically severe nature of the underlying disease, with relatively high mortality and transplantation rate, we wanted to follow the renal function during the course of the liver disease. To the best of our knowledge, there are very few studies on long-term follow-up of renal function with measured GFR in patients with CLD.

2 | PATIENTS

The study was approved by the Regional Ethical Review Board in Stockholm (ref: 2016/1615-31/2).

This analysis was based on the patients in our tertiary referral centre, and the patients were either investigated on a single occasion or were followed entirely by our group depending on agreement with the referral unit. We included patients younger than 20 years of age who were investigated for CLD in our unit during the past three decades. Children with liver tumours and chronic viral hepatitis were excluded because of the possible direct renal impact of the disease or its treatment. However, we included patients with Alagille syndrome (AGS), since this disease is mostly regarded as a primary cholestatic disorder.

In all, 1002 investigations of renal function were performed in 289 patients. The patients were followed for 0–17.9 years; 84 were followed for at least 5 years, 41 for at least 8 years and 19 for at least 10 years. During the study period, 67 patients underwent liver transplantation (LTX) and another 13 patients died. The follow-up for the purpose of this study was carried on until the patient received a LTX or reached 20 years of age or died. Of the totally 80 patients who underwent LTX or died, 77 had their last GFR investigation performed within less than a year before that event.

Patient characteristics are given in Table 1. The patients had numerous discordant diagnoses which were pooled into the following diagnostic groups: (1) biliary atresia (BA); (2) intrahepatic cholestasis (IHCS) comprising AGS, progressive familial intrahepatic cholestasis (PFIC), primary sclerosing cholangitis (PSC) and other forms of IHCS of unknown aetiology (MISC); (3) metabolic liver disease (MET) comprising glycogen storage disease (GSD), alpha-1-antitrypsin deficiency with liver damage (AATD) and single cases of different metabolic disorders (MISC); (4) autoimmune hepatitis (AIH); (5) vascular liver disorders (VASC); (6) cryptogenic cirrhosis (CC); and (7) acute fulminant liver failure (AFL).

Based on the diagnostic groups, the patients were also classified as cholestatic (BA + IHCS) and non-cholestatic (MET and AIH) cases.

3 | METHODS

3.1 | Kidney function

GFR was tested by clearance of inulin (Inutest, 25%, Fresenius Kabi Austria GmbH, Graz, Austria) by standard clearance technique during water diuresis and continuous infusion. In the youngest children who were not able to empty their bladder on request, clearance was performed by single injection technique with repeated blood samples. Inulin concentration in the plasma and urine was determined by the anthrone method and later by the enzymatic technique. Body surface area was computed from height and weight using the formula of Haycock et al.

After the cost of inulin increased tenfold in the year 2000, the method of measuring GFR was changed to clearance of iohexol by single injection technique. An i.v. injection of 5 ml (or 0.3 ml/kg in small children) iohexol (Omnipaque, 300 mg/ml, GE Healthcare, Stockholm, Sweden) was given, and blood samples were drawn from the contralateral arm after 180, 200, 220 and 240 min. Clearance was calculated from the slope of the plasma concentrations using a one-compartment model corrected by the Bröchner-Mortensen formula. The plasma concentration of iohexol was determined by high-performance liquid chromatography.

In connection with the clearance investigations, blood pressure was measured as well as urine analyses regarding proteinuria.

A total of 67 healthy children, median age 10.6 (6.1; 14.2) years, were investigated by clearance of inulin to serve as controls for renal function. Their mean (SD) GFR was 116 (11) ml/min/1.73 m². Hyperfiltration was defined as > +2 SD of that of controls (>138).

3.2 | Statistical evaluation

Data on age and follow-up time are presented as median (interquartile range IQR, meaning 25th–75th percentile). GFR is expressed as mean and standard deviation (SD). Differences in mean GFR at baseline between groups were tested using two-sample t-tests. Mean GFR at first and last investigation of patients who finally lost their native liver due to liver transplantation or death was compared by conducting paired t-tests. Unadjusted linear mixed-effects regression models were used to investigate the yearly change in GFR.
TABLE 1 Patient characteristics in different main groups, subgroups, number investigated, (number investigated more than once), number transplanted [LTX], number dead, age at first inv., follow-up time for all and for those investigated more than once

| Diagnosis     | Number (inv.) | LTX | Dead | Age at first inv | Follow-up time (all) | Follow-up time (> 1 inv.) |
|---------------|--------------|-----|------|------------------|----------------------|--------------------------|
|               |              |     |      | Median (IQR), years | Median (IQR), years | Median (IQR), years     |
| All           | 289 (193)    | 67  | 13   | 9.3 (3.7–14.3)   | 2.6 (0.0–6.0)        | 4.9 (2.6–7.7)            |
| BA            | 46 (27)      | 21  | 7    | 1.4 (0.7–2.8)    | 0.8 (0.0–6.9)        | 5.9 (2.1–8.8)            |
| IHCS          | 67 (42)      | 22  | 2    | 5.8 (1.8–12.0)   | 3.3 (0.0–7.0)        | 6.4 (3.7–9.0)            |
| PSC           | 21 (14)      | 4   |      | 12.0 (8.9–15.4)  | 4.6 (0.0–6.0)        | 5.4 (4.6–6.6)            |
| PFIC          | 18 (12)      | 9   |      | 3.3 (1.9–9.2)    | 8.7 (0.0–9.0)        | 9.3 (8.7–10.6)           |
| AGS           | 23 (15)      | 9   |      | 2.6 (1.1–6.4)    | 1.5 (0.0–6.3)        | 5.6 (1.5–7.0)            |
| MISC          | 5            |     | 2    |                  |                      |                          |
| MET           | 48 (29)      | 13  | 3    | 4.7 (2.4–9.8)    | 2.5 (0.0–6.3)        | 5.6 (4.0–9.6)            |
| AATD          | 10 (9)       | 7   |      | 5.1 (1.9–10.9)   | 4.7 (4.0–9.6)        | 5.3 (4.0–9.6)            |
| GSD           | 20 (13)      | 2   |      | 4.8 (2.8–8.6)    | 4.2 (0.0–5.9)        | 5.6 (4.4–7.7)            |
| MISC          | 18           | 4   | 3    |                  |                      |                          |
| AIH           | 104 (81)     | 6   |      | 14.5 (12.4–16.5) | 2.6 (0.9–5.4)        | 3.7 (2.3–6.4)            |
| VASC          | 11 (9)       | 1   |      | 7.1 (2.1–7.8)    | 4.3 (0.7–5.4)        | 4.9 (4.0–5.4)            |
| CC            | 8 (4)        | 3   | 1    | 12.0 (10.2–14.9) | 0.8 (0.0–2.4)        | 2.4 (1.8–6.6)            |
| AFL           | 5 (1)        |     |      | 12.3 (3.0–12.4)  | 0.0 (0.0–0.0)        | 1.7 (1.7–1.7)            |
| Cholestatic   | 113 (69)     | 54  |      | 2.8 (1.3–8.9)    | 2.2 (0.0–6.9)        | 6.0 (3.3–9.0)            |
| Noncholestatic| 152 (110)    | 23  |      | 13.1 (7.5–16.0)  | 2.6 (0.0–5.8)        | 4.3 (2.5–6.6)            |

Note: Five cholestatic and 18 MET patients with widely discordant diagnoses (MISC) were not included into the subgroup analyses. Abbreviations: AATD, alpha-1-antitrypsin deficiency; AFL, acute fulminant liver failure; AGS, Alagille’s syndrome; AIH, autoimmune hepatitis; BA, biliary atresia; CC, cryptogenic cirrhosis; GSD, glycogen storage disease; IHCS, intrahepatic cholestasis; MET, metabolic liver disease; MISC, miscellaneous; PFIC, progressive familial intrahepatic cholestasis; PSC, primary sclerosing cholangitis; VASC, vascular liver disease.

Throughout the years of follow-up for all diagnostic groups combined and for each subgroup separately. The models allowed for a random intercept for each child to account for potential correlation among repeated values of GFR over time. In order to formally test the difference between children with initial hyperfiltration and those with a normal or low GFR, a binary variable for hyperfiltration and an interaction term with the continuous variable for the years of follow-up were added to the models. Differences in the change over time were evaluated based on a Wald chi-squared test. Two-sided p-values were reported. All statistical evaluations were conducted using STATA 15 (StataCorp, College Station, Texas 77845 USA).

4 | RESULTS

None of the patients had hypertension or albuminuria.

Table 1 gives the total number of patients investigated, those investigated more than once and patients who were transplanted or died during the observation period. Age at first investigation and time of follow-up for all patients and for those investigated more than once are also given in the table.

Table 2 gives the mean (SD) GFR at first investigation and after at least 5, 8 and 10 years in the different groups, as well as in the cholestatic versus non-cholestatic diagnoses. At the first investigation, patients with BA and MET and non-cholestatic diagnoses had significantly higher GFR than the controls. MET patients had significantly higher GFR than patients with IHCS and those with AIH. Among the IHCS patients, those with PSC had significantly higher and those with AGS significantly lower GFR than the controls. Patients with AGS had significantly lower GFR than those with PSC and those with PFIC. In patients with MET, the children with GSD had significantly higher GFR than those with AATD.

Table 3 presents the yearly change in GFR based on clearance of inulin or iohexol in all patients and in the different diagnostic groups. It also gives the change in GFR in those patients hyperfiltering at first investigation compared to those with a baseline GFR within normal range. The greatest fall in GFR was seen in patients with MET, especially those with GSD, and in patients with AIH. There was also significantly greater fall in GFR in all main groups hyperfiltering at start.

When comparing the different groups with regard to time of follow-up, the change in GFR in patients with AIH was significantly greater than in patients with BA (p = 0.015) or IHCS (p = 0.003). Moreover, the change in GFR was significantly greater (p = 0.002) in patients with non-cholestatic liver disease than in those with cholestasis.

Table 4 shows the initial and final GFR of the patients who lost their native liver due to transplantation or death as well as the time between the first and last investigation of the different diagnostic groups. The GFR remained stable in all groups, despite several years between the investigations.
Table 2: Mean (SD) GFR at baseline, after at least 5, 8 and 10 years in the different diagnostic groups, subgroups and in cholestatic and non-cholestatic diseases

| Diagnoses   | At baseline | After 5 years | After 8 years | After 10 years |
|-------------|-------------|---------------|---------------|---------------|
|             | N           | Mean (SD)     | n             | Mean (SD)     | n             | Mean (SD)     |
| BA          | 46          | 127 (34)      | 12            | 131 (30)      | 9             | 116 (23)      | 2             | 117 (12)      |
| IHCS        | 67          | 120 (43)      | 26            | 115 (29)      | 13            | 122 (24)      | 7             | 112 (31)      |
| PSC         | 21          | 133 (40)      | 7             | 120 (22)      | 1             | 1              | 150           |
| PFIC        | 18          | 135 (46)      | 11            | 128 (31)      | 11            | 125 (24)      | 4             | 109 (29)      |
| AGS         | 23          | 102 (33)      | 8             | 92 (18)       | 2             | 107 (26)      | 2             | 98 (38)       |
| MET         | 48          | 146 (49)      | 15            | 122 (21)      | 7             | 121 (29)      | 6             | 134 (18)      |
| AATD        | 10          | 128 (39)      | 4             | 104 (11)      | 2             | 87 (2)        | 1             | 117           |
| GSD         | 20          | 177 (50)      | 7             | 136 (16)      | 3             | 143 (12)      | 3             | 146 (17)      |
| AIH         | 104         | 118 (30)      | 27            | 102 (23)      | 9             | 106 (16)      | 3             | 90 (10)       |
| VASC        | 11          | 112 (27)      | 4             | 104 (16)      | 2             | 96 (16)       | 0             |
| CC          | 8           | 121 (32)      | 0             | 1             | 127           | 1             | 107           |
| AFL         | 5           | 144 (14)      | 0             | 1             | 127           | 1             | 107           |
| Total       | 289         | 125 (38)      | 84            | 114 (27)      | 41            | 116 (23)      | 19            | 115 (26)      |

Note: $\text{p} < 0.023$ vs controls, $\text{p} < 0.001$ vs controls, $\text{p} = 0.001$ vs controls, $\text{p} = 0.046$ vs controls, $\text{p} = 0.048$ vs controls, $\text{p} = 0.026$ IHCS vs MET, $\text{p} = 0.002$ AIH vs MET, $\text{p} = 0.010$ PSC vs AGS, $\text{p} = 0.042$ PFIC vs AGS, $\text{p} = 0.046$ GSD vs AATD.

Abbreviations: AATD, alpha-1-antitrypsin deficiency; AFL, acute fulminant liver failure; AGS, Alagille’s syndrome; AIH, autoimmune hepatitis; BA, biliary atresia; CC, cryptogenic cirrhosis; GSD, glycogen storage disease; IHCS, intrahepatic cholestasis; MET, metabolic liver disease; PFIC, progressive familial intrahepatic cholestasis; PSC, primary sclerosing cholangitis; VASC, vascular liver disease.

Figure 1a and b gives the GFR trajectories over time in all patients (1a) as well as in the cholestatic versus non-cholestatic ones (1b).

5 | DISCUSSION

Since this study was performed in a tertiary referral centre, we did not aim to draw any epidemiological conclusions. However, the relatively high rate of mortality or need for LTX does indicate that we report on a representative material, covering the whole scope of paediatric CLD. In an earlier study, we reported our findings at the first investigation of newly detected, untreated children with CLD. We could not follow all of the patients whom we initially investigated, since we did not receive a referral for long-term care of all children. Moreover, the duration of the follow-up period was dependent on the biological nature of the liver disease. Thus, the adolescents with newly onset AIH were 10–15 years older than the infants with BA and had to be transferred to adult units after a shorter follow-up.

Our earlier study showed an unexpectedly well-maintained initial kidney function in untreated children with CLD. In the present study, we found that in most cases this remained so for a long time during the course of the CLD. According to our study design, we followed the renal function annually, and thus, we could not predict the onset of the liver decompensation. Thus, declining renal function could not predict poor outcome of the liver disease.

Diagnostic groups with initially high GFR, such as GSD and AIH, had decreasing renal function during the follow-up period, although it only rarely reached pathological levels, that is, a GFR below 75 ml/min/1.73 m². Hyperfiltration is known to occur in early GSD and is regarded as an early phase of progressive renal damage. Microscopically, this is reflected by focal segmental glomerulosclerosis. Glomerular hyperfiltration is a well-known finding in patients with diabetes and has been claimed to be a prognostic factor for declining renal function and development of diabetic nephropathy, possibly followed by renal failure.

GSD-induced error of lipid metabolism causes intracellular lipid accumulation that might lead to both liver and kidney damage. Optimal metabolic control is regarded as the principle way of preventing renal deterioration. Activation of lipid metabolism by PPARα agonists such as fenofibrate might be a pharmacological alternative for the prevention of renal damage in GSD. Among our 20 patients with GSD only those with initial hyperfiltration showed significant fall in their GFR during the observation period, that is, during their childhood and adolescence.

When we divided our patients into cholestatic versus non-cholestatic diagnostic groups, we found that the cholestatic patients had a more stable renal function than the non-cholestatic ones (Figure 1a and b). This seems to be paradoxical. Nevertheless, the kidneys have an active role in the bile acid metabolism, in both...
The kidneys have two major bile acid receptors: the nuclear receptor of farnesoid X receptor (FXR) and the membrane-bound Takeda G-protein receptor 5 (TGR5). Activation of these receptors has been found to be nephroprotective, at least in animal models. Moreover, sulphation, which is one of the most important bile acid detoxification steps, takes place in the kidneys. Cholestasis has also been found to upregulate certain hepatocellular synthetic functions, for example, that of certain coagulation factors. Thus, the general adaptation to cholestasis may have a beneficial effect on renal function.

AGS is a chronic cholestatic disease that often has associated renal involvement of varying nature and grade. No genotype-phenotype correlation has been found. Unlike the rest of the cholestatic patients in this study, the children with AGS had a relatively low initial GFR followed by a further decreasing tendency, implying that the virtual protective role of chronic cholestasis could not counterbalance the disease-specific slow progress of deteriorating kidney function.

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For the purpose of this study, we regarded transplantation and death (i.e. both forms of native organ loss) to be equivalent outcomes among the patients with the most rapid progression of disease. Renal function in these patients remained stable throughout the follow-up period, similarly to the more benign groups. In all of these patients, the last renal investigation was performed less than one year before the loss of the native liver or the patient, respectively. The circumstances of possible acute or subacute renal damage developing during the end-stage liver disease of these patients are beyond the scope of the present study.

The main strength of this study is that we used accurate methods for measuring GFR, rather than estimating it. The best method of measuring GFR is by clearance of inulin, which is regarded as the gold standard. Good agreement between the clearance of inulin and iohexol. However, we have previously shown that in 60 children investigated simultaneously with both methods, there was a good agreement between the clearance of inulin and iohexol.
The data clearly confirm the earlier finding that hyperfiltration can only be revealed by measuring and not estimating GFR. A further strength is that we followed the renal function in children representing the whole spectrum of paediatric CLD and that we did this according to a standardised protocol at regular intervals and correlated the data to the course of the CLD.

A limitation is that we did not follow measured GFR prospectively during the terminal progression of the liver disease.

### TABLE 4

Development of GFR (ml/min/1.73 m²) in the patients who finally lost their native liver due to liver transplantation (LTX) or death. Values at first and last investigation and the time in years elapsed between the two

| Diagnosis     | Number | GFR at first investigation | GFR at LTX/death | Paired t-test | Time in between |
|---------------|--------|---------------------------|------------------|---------------|-----------------|
|               |        | Mean (SD) | Mean (SD) | p  | Median (IQR) years |
| All           | 80     | 128 (47) | 122 (41) | 0.107 | 3 (0; 9) |
| BA            | 28     | 130 (38) | 121 (30) | 0.058 | 3 (0; 7) |
| IHCS          | 24     | 120 (56) | 122 (56) | 0.861 | 3 (0; 11) |
| PSC           | 4      | 158 (58) | 144 (30) | 0.494 | 7 (4; 11) |
| PFIC          | 9      | 136 (63) | 159 (62) | 0.284 | 0 (0; 9) |
| AGS           | 9      | 97 (40)  | 84 (28)  | 0.274 | 3 (0; 16) |
| MET           | 16     | 139 (56) | 126 (49) | 0.128 | 5 (2; 8) |
| AATD          | 7      | 135 (45) | 110 (15) | 0.184 | 6 (4; 8) |
| GSD           | 2      | 234 (66) | 220 (86) | 0.50  | 5 (5; 5) |
| MISC          | 5      |           |           |     |                 |
| AIH           | 7      | 126 (38) | 119 (21) | 0.648 | 2 (0; 7) |
| VASC          | 1      | 121      | 139      |     |                 |
| CC            | 4      | 123 (29) | 107 (20) | 0.263 | 3 (1; 10) |
| Cholestatic   | 52     | 125 (47) | 122 (43) | 0.459 | 3 (0; 9) |
| Non-cholestatic | 23  | 135 (51) | 124 (42) | 0.124 | 4 (1; 8) |

Note: Two cholestatic and 4 MET patients with widely discordant diagnoses (MISC) were not included into the subgroup analyses.

Abbreviations: AATD, alpha-1-antitrypsin deficiency; AFL, acute fulminant liver failure; AGS, Alagille’s syndrome; AIH, autoimmune hepatitis; BA, biliary atresia; CC, cryptogenic cirrhosis; GSD, glycogen storage disease; IHCS, intrahepatic cholestasis; MET, metabolic liver disease; MISC, miscellaneous; PFIC, progressive familial intrahepatic cholestasis; PSC, primary sclerosing cholangitis; VASC, vascular liver disease.

### FIGURE 1

GFR (± CI) (ml/min/1.73 m²) in relation to follow-up time in Fig 1a all patients (solid line) and in Fig 1b cholestatic (solid line) and noncholestatic (dotted line) patients.
6 | CONCLUSION

We can conclude that, unlike in adults, paediatric CLD has less impact on renal function and in our long-term follow-up the kidney function remained stable, as long as the liver disease was compensated. Hyperfiltration seemed to be the only reliable prognostic marker of declining renal function. In the diagnostic groups which had initial hyperfiltration, the GFR did decrease but only rarely reached pathological levels.

CONFLICT OF INTEREST

None declared.

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