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ORIGINAL ARTICLE

Hepascore predicts liver outcomes and all-cause mortality in long-term methotrexate users: A retrospective cohort study

Zhengyi Wang,*,† Yi Huang,*,† Hans Nossent,*,‡ Jonathan J Chan,§ Leon A Adams,*,† John Joseph,¶ Wendy Cheng,‖ George Garas,† Gerry MacQuillan*,† and Gary P Jeffrey*,†

*School of Medicine and Pharmacology, The University of Western Australia, Departments of †Hepatology, ‡Rheumatology, §Dermatology, Sir Charles Gairdner Hospital, ¶Department of Biochemistry, PathWest Laboratory Medicine and ‖Department of Gastroenterology and Hepatology, Royal Perth Hospital, Perth, Western Australia, Australia

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Correspondence
Professor Gary P Jeffrey, School of Medicine, The University of Western Australia (M503), 35 Stirling Highway, Crawley, WA 6009, Australia.
Email: gary.jeffrey@uwa.edu.au

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Abstract

Background and aim: Methotrexate (MTX) is routinely used for immunological disorders, and its long-term use is associated with hepatotoxicity. The aim of this study was to investigate whether a serum liver fibrosis test (Hepascore) predicted the risk of adverse liver-related outcomes and mortality.

Methods: A total of 92 patients in Western Australia who had a long-term MTX intake history,from 2004 to 2016, were recruited and followed up from the first Hepascore to death or end of the study. Clinical data, all deaths, and liver-related outcomes (liver-related death and decompensation) were obtained from hospital, PathWest, and WA Data Linkage Unit databases.

Results: Nine deaths and four adverse liver-related outcomes occurred during the follow up of 354 person-years. The 5-year survival was 86.1%. The liver-related outcome free survival was 95.6%. Baseline Hepascore ≥0.84 was associated with advanced fibrosis on liver biopsy ($P = 0.025$). A baseline Hepascore ≥0.84 was significantly associated with higher risks for adverse liver-related outcomes ($P < 0.001$) and all-cause mortality ($P = 0.001$). Cox regression demonstrated that only baseline Hepascore ≥0.84 was independently associated with the increased risk of all-cause mortality (7.91 [1.52–41.29], $P = 0.014$). Moreover, any Hepascore ≥0.84 found during follow up was independently associated with the increased risk of all-cause mortality (86.18 [4.03–1844.83], $P = 0.007$).

Conclusions: This study demonstrated the potential importance of Hepascore monitoring in long-term MTX users. Patients with a Hepascore higher than 0.84 at any stage had increased mortality, but further studies are required to confirm this finding.

Introduction

Methotrexate (MTX) is a first-line disease-modifying drug (DMARD) used to treat several immunological disorders that include psoriasis and rheumatoid arthritis (RA). Drug-induced liver injury (DILI) is a common adverse side effect of MTX therapy.[1] Acute hepatotoxicity related to MTX use occurs in 15% of patients and is characterized by elevated liver enzymes and is often self-limiting and reversible with ongoing use of MTX.[2,3] Chronic hepatotoxicity includes histological changes of fatty liver disease, fibrosis, and cirrhosis. It is estimated that up to 20% of psoriasis patients have advanced liver fibrosis after 2 years of MTX therapy,[4] which progresses to liver decompensation and death.[5] Guidelines of MTX usage are different between countries and indications. The previous U.S. guidelines for psoriasis recommended liver biopsy after a cumulative dose of 1.5 g,[6] whereas the more recent guidelines recommended avoidance of MTX in patients with cirrhosis and hepatitis.[7] UK guidelines recommended monitoring serum procollagen III levels to exclude liver fibrosis or cirrhosis in patients taking long-term MTX.[8] European guidelines for RA recommended liver function test (LFT) monitoring for the surveillance of hepatotoxicity and only recommended liver biopsy in patients with persistently high transaminase values despite discontinuation of treatment.[9] However, the use of routine liver biopsy is controversial as it is invasive, costly, and has significant potential complications. Aithal GP *et al.* reported the incidence of significant fibrosis to be 0, 2.6, 2.6, 8.2, and 8.2% at cumulative doses of 1.5, 3, 4.5, 5, and 6 g, respectively. The reported low incidence of significant fibrosis also questions the necessity of liver biopsy.[10,11]

Noninvasive serum models to detect liver fibrosis have been developed to replace the need for liver biopsy to evaluate for liver fibrosis and cirrhosis. Serum procollagen III aminoterminal propeptide (PIIINP) was initially developed to predict liver fibrosis in psoriasis patients receiving long-term

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MTX therapy.[12,13] However, conflicting results regarding the accuracy of PIIINP in predicting liver fibrosis have been reported.[12,14] Hepascore is a serum fibrosis model that uses bilirubin, α2-macroglobulin, hyaluronic acid, and γ-glutamyl transpeptidase to calculate a score.[15] It has been shown to accurately assess the severity of liver fibrosis in non-alcoholic liver disease, chronic hepatitis B, and alcoholic liver disease.[16] Importantly, Hepascore was demonstrated to predict the risk of long-term liver decompensation, liver-related death, and all-cause mortality.[17] Therefore, the aim of this study was to evaluate the effectiveness of Hepascore in predicting adverse liver-related outcomes and all-cause mortality in a cohort of patients on long-term MTX therapy.

Methods

Study population. All patients with a history of long-term MTX therapy who had undergone a Hepascore test in Western Australia from 2004 to 2016 were retrospectively recruited. A total of 92 patients were included in the final analysis. This study was approved by Sir Charles Gairdner Hospital Human Research Ethics Committee, the Data linkage unit, and the Western Australia Department of Health Human Research Ethics Committee.

Clinical data collection. Data from all patients included age, gender, and Hepascore values, which were tested in a single center (PathWest, WA). A subset of 35 patients had more detailed clinical data. Ethnic groups were defined as Caucasian, Asian, Middle Eastern, or other. This included disease indication for MTX therapy (psoriasis, RA, others), MTX cumulative dose (gm), years of intake, coexisting liver disease (non-alcoholic fatty liver disease, alcoholic fatty liver disease, and viral hepatitis) and comorbidities (diabetes mellitus, hypertension, and dyslipidemia). Liver biopsy was performed in 16 patients who were believed to have clinically significant liver fibrosis. Liver biopsy fibrosis severity was staged using the Metavir system (stages 0–4). The serum Hepascore value is calculated using the following formula.[15]

$$y = \exp[-4.185818 - (0.0249 \times \text{age}) + (0.7464 \times \text{sex}) + (1.0039 \times \alpha 2\,\text{macroglobulin}) + 0.0302 \times \text{hyalurionc acid}] + (0.0691 \times \text{bilirubin}) - (0.0012 \times \gamma GT)];$$

$$\text{Hepascore} = \frac{y}{1+y},$$

with age provided in years; male gender = 1, female gender = 0; and α2-macroglobulin in g/L, hyaluronate in μg/L, bilirubin in μmol/L, and γGT in U/L.

A Hepascore value ≥0.84 indicates the likely presence of liver cirrhosis on liver biopsy confirmed by our previous study.[15]

Follow up. Long-term follow up was performed using the Western Australian Data Linkage Unit, which links the state cancer registration, in-patient hospital morbidity, and death record.[18] International Statistical Classification of Diseases and Related Health Problems (ICD) 10 (after 1997) classification codes were used for hospital admission diagnosis and cause of death. Patients were followed from the day of first Hepascore tested (baseline) to each end-point or the end of study.

Clinical outcome definition. The clinical outcomes identified by ICD-10 were obtained from the WA Data Linkage Unit databases. Outcomes included all-cause mortality, liver-related death (LRD; death from liver failure (K72.1), variceal bleeding (I98.3), hepatocellular carcinoma (C22.0), or liver disease as the major contributing factor), liver transplantation (WA liver transplantation record), liver decompensation (ascites (R18), hepatic encephalopathy (K72.1), variceal bleeding (I98.3), hepatorenal syndrome (K76.7), or spontaneous bacterial peritonitis (L65.0)). Composite liver-related outcome was a combined end-point of liver decompensation and LRD, whichever happened first.

Statistical analysis. All data analyses were performed with SPSS v. 23 (SPSS Inc., Illinois, United States). Data were presented as mean ± standard deviation (SD), median (interquartile range), or number (percentage) where appropriate. One-way ANOVA or χ^2 analysis was used to compare the difference between groups where appropriate. Clinical outcomes were compared by survival curves (Kaplan–Meier analysis). Multivariable logistic and proportional hazards model (Cox regression) were used to analyze the association between variables and the risk of clinical outcomes. Odds ratio (OR) and hazard ratio (HR) with 95% confidence interval (CI) were calculated. A p value <0.05 was defined as statistically significant.

Results

Study population. A total of 92 patients were included in the study. The mean age was 57.4 ± 13.4 years, and 52 were males (54.2%). The mean follow up was 46.2 months (range: 1–128 months) with 354 person-years. The median Hepascore was 0.39 (interquartile range: 0.16–0.80). There was no significant differences in gender distribution or ethnicity in those with Hepascore value <0.84 and those with a value ≥0.84 (Table 1). At the end of the study, four patients had liver decompensation, and nine patients died. There were two liver-related deaths, three deaths due to infection (one pneumonia sepsis, one intestinal pseudo-obstruction and sepsis, and one psoas abscess), two cardiovascular deaths, one metastatic lung cancer, and one uncertain cause. The overall 5-year survival rate for patients with long-term MTX exposure was 86.1%, and the 5-year liver-related free survival was 95.6%.

Detailed clinical data were available in 35 patients (Table 1). The most common indications for MTX treatment were psoriasis (48.6%) and RA (40%). The mean duration of MTX treatment was 7.8 ± 6.2 years, and the mean cumulative dose was 5.48 ± 4.92 grams. Of the 17 patients with psoriasis, 8 had psoriasis (PsO), and 9 had psoriatic arthritis (PsA). There was no significant difference in MTX cumulative dosage (P = 0.896) or total mortality (P = 0.953) between these groups. Of the 35 patients, 16 ceased MTX treatment, and 8 of these were due to persistently elevated Hepascore and/or LFT, advanced fibrosis, or cirrhosis on liver biopsy. Coexisting liver disease was present in 19 of 35 patients. Non-alcoholic fatty liver disease (NAFLD) was the most common (37.1%), whereas alcoholic liver disease was present in 8.6%, hepatitis B in 2.9%, and

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Table 1 Patient characteristics and baseline Hepascore

	Total	Hepascore < 0.84	Hepascore ≥ 0.84	*P* value
Total cohort				
Number	92	70	22	
Male, *n* (%)	52 (56.5)	43 (61.4)	9 (40.9)	0.074
Age, years	57.4 ± 13.4	54.3 ± 12.7	67.2 ± 10.9	< 0.001
Total bilirubin (μmol/L)	11.3 ± 13.5	9.4 ± 5.0	17.3 ± 25.6	0.015
GGT (U/L)	104.6 ± 185.9	63.5 ± 81.8	235.3 ± 322.9	< 0.001
Clinical outcomes, *n* (%)				
Decompensated cirrhosis	4 (4.3)	0 (0.0)	4 (18.2)	0.003
Composite liver-related outcome[†]	4 (4.3)	0 (0.0)	4 (18.2)	0.003
Total mortality	9 (12.5)	3 (4.3)	6 (27.3)	0.005
Liver-related mortality	2 (2.2)	0 (0.0)	2 (9.1)	0.006
CVD-related mortality	2 (2.2)	0 (0.0)	2 (9.1)	
Cancer-related mortality[‡]	2 (2.2)	1 (1.4)	1 (4.5)	
Other cause mortality[§]	3 (3.4)	2 (2.9)	1 (4.5)	
Subgroup with complete clinical data				
Number	35	24	11	
Ethnicity, Caucasian, *n* (%)	33 (94.3)	22 (91.7)	11 (100)	0.615
Major disease for MTX treatment				
Psoriasis, *n* (%)	17 (48.6)	14 (58.3)	3 (27.3)	0.148
Rheumatoid arthritis, *n* (%)	14 (40.0)	7 (29.2)	7 (63.6)	
Others,[¶] *n* (%)	4 (11.4)	3 (12.5)	1 (9.1)	
MTX intake years, years	7.8 ± 6.2	7.0 ± 4.5	9.4 ± 9.0	0.309
Cumulative MTX dosages, gm	5.48 ± 4.92	5.42 ± 4.01	5.61 ± 6.73	0.918
Ever stopped MTX due to liver cause	8 (22.9)	3 (12.5)	5 (45.5)	0.077
Liver biopsy, *n* (%)	16 (45.7)	9 (37.5)	7 (63.6)	0.273
Coexisting liver disease,[††] *n* (%)				
NAFLD	13 (37.1)	9 (37.5)	4 (36.4)	0.409
ALD	3 (8.6)	2 (8.4)	1 (4.5)	
HBV	1 (2.9)	1 (4.2)	0 (0)	
HCV	1 (2.9)	0 (0)	1 (4.5)	
Others	1 (2.9)	1 (4.2)	0 (0)	
Co-morbidity, *n* (%)				
Diabetes	13 (37.1)	8 (33.3)	5 (50.0)	0.451
Hypertension	17 (48.6)	10 (41.7)	7 (70.0)	0.259
Dyslipidemia	18 (51.4)	10 (41.7)	8 (72.7)	0.146
Medication				
Steroids, *n* (%)	7 (20.0)	4 (16.7)	3 (27.3)	0.652
Other DMARD, *n* (%)	7 (20.0)	4 (16.7)	3 (27.3)	0.652
ALT (U/L)	52.8 ± 33.1	51.1 ± 24.3	52.4 ± 47.4	0.920
ALP (U/L)	91.0 ± 38.7	87.1 ± 41.4	100.3 ± 34.5	0.369
Albumin (g/L)	40.9 ± 4.2	42.7 ± 2.3	37.1 ± 4.9	< 0.001

[†]Composite liver-related outcome included decompensated liver cirrhosis and liver-related mortality.

[‡]Excluding liver cancer.

[§]Three patients died from other causes: one intestine obstruction and sepsis, one psoas abscess (Hepascore ≥0.84), and one unknown.

[¶]Other MTX indication disease included juvenile idiopathic arthritis (*n* = 1), palmar pomphoylyx (*n* = 1), atopic actinic dermatitis (*n* = 1), and sarcoidosis (*n* = 1).

[††]Coexisting liver disease was defined as any liver diseases other than MTX-induced liver injury, diagnosed during follow up based on clinical evidence and/or histological results.

Data were presented as mean ± SD or cases (percentage), and P values were analyzed by one-way ANOVA or chi-square analysis.

ALD, alcoholic liver disease; ALP, alkaline phosphatase; ALT, alanine aminotransferase; CVD, cardiovascular disease; DMARD, disease-modifying antirheumatic drugs; GGT, γ-glutamyl transpeptidase; HBV, hepatitis B; LFT, liver function test; MTX, methotrexate; NAFLD, non-alcoholic fatty liver disease.

hepatitis C in 2.9%. There was no significant difference in the presence of NAFLD between psoriasis and RA patient groups (41.2% *vs* 42.9%. $P = 1.000$) or between PsO and PsA (50.0 *vs* 80.0%, $P = 0.501$). The presence of a metabolic disorder was common as 13 (37.1%) had type 2 diabetes, 17 (48.6%) had hypertension, and 18 (51.4%) had dyslipidemia. Seven patients (20%) received steroids or other DMARDs at the same time as MTX. Among 16 patients who had a liver biopsy due to the

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presence of clinically suspected significant liver fibrosis, 7 had advanced fibrosis (43.7%), and 3 had cirrhosis (18.7%). A Hepascore ≥0.84 was found in five of seven patients with advanced fibrosis and all three cirrhotic patients. Duration of MTX use and cumulative dose of MTX were not significantly different between Hepascore <0.84 and those ≥0.84. The rate of cessation of MTX due to a liver cause was higher in the Hepascore ≥0.84 group; however, this did not reach statistical significance (12.5 *vs* 45.5%, $P = 0.077$). There was also no difference in the presence of coexisting liver diseases, metabolic disorders, steroids, or other DMARD use. Bilirubin and gamma-glutamyl transferase (GGT) were both significantly elevated in the Hepascore ≥0.84 group ($P = 0.015$ and $P < 0.001$), whereas albumin was significantly lower compared with Hepascore <0.84 ($P < 0.001$). Proportions of advanced fibrosis and cirrhosis were also both significantly higher in the Hepascore ≥0.84 group ($P = 0.025$ and $P = 0.021$).

Hepascore and clinical outcomes. Patients with a baseline Hepascore ≥0.84 had a significantly increased number of liver-related outcomes compared to those with a Hepascore <0.84 (log-rank $P = 0.001$; Fig. 1). Liver decompensation and LRD occurred in 18.2 and 9.1% of those with a Hepascore ≥0.84, respectively. No patient with a Hepascore <0.84 had any liver-related outcome. The all-cause mortality rate was also significantly higher in patients with a baseline Hepascore ≥0.84 (Table 1; 4.3 *vs* 27.3%, $P = 0.005$). Twenty-one patients had a follow-up Hepascore test performed with at least a 12-month interval between each test.[19] When patients with Hepascore ≥0.84 at baseline or during follow up were combined, the significant increased risk of liver-related outcome (log-rank $P = 0.001$) and all-cause mortality (log-rank $P = 0.003$) remained. Any Hepascore ≥0.84 was also independently associated with the increased risk of all-cause mortality (86.18 [4.03–1844.83], $P = 0.007$). In a subgroup of patients with a baseline Hepascore <0.84 and a stable or lower Hepascore on repeat testing ($n = 11$), none had any adverse liver-related outcome. Among these patients, the mean MTX duration was 7.64 ± 5.12 years, and cumulative dose was 5.29 ± 2.72 gm. Two patients died—one from lung cancer and the other from infection.

Cox regression in those 35 patients with detailed clinical information found that a baseline Hepascore ≥0.84 increased the risk of all-cause mortality by 7.91 times (HR and 95% CI: 7.91 [1.52–41.29], $P = 0.014$), and this remained significant after multivariable adjustment (184.4 [5.71–5958.5], $P = 0.003$) (Table 2). RA *versus* psoriasis (0.18 [0.03–1.01], $P = 0.052$), dyslipidemia (0.14 [0.02–1.43], $P = 0.098$), and steroid use (0.09 [0.01–1.58], $P = 0.099$) were not significantly associated with all-cause mortality.

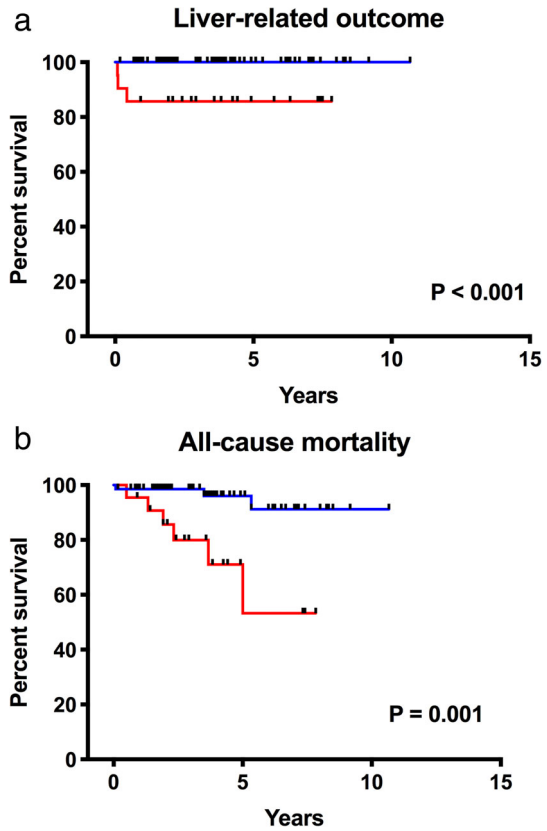

Figure 1 Hepascore predicts clinical outcomes in long-term methotrexate users ($n = 92$). (a) Cumulative rates of patients free from liver-related outcome, log-rank $P < 0.001$. (b) Cumulative rates of patients survived from total mortality, log-rank $P = 0.001$; blue: patients with an Hepascore <0.84; red: patients with an Hepascore ≥0.84.

Discussion

This study presents the risks of adverse clinical outcomes in 92 patients taking long-term MTX while being monitored for hepatic fibrosis with Hepascore. Patients with Hepascore ≥0.84 also have increased rates of adverse liver-related outcomes, including liver decompensation and/or LRD. A significant association between baseline Hepascore and all-cause mortality was also found in this study.

Overall, the risk of liver decompensation or LRD in long-term MTX users was small, with a 5-year free liver-related outcome survival of 95.6%. A recent meta-analysis of 28 studies concluded that MTX use for more than 24 weeks did not affect the short-term risk for liver decompensation or LRD compared to other agents.[20] However, the severity of liver fibrosis in patients, measured either by liver biopsy or serum fibrosis markers, was not available. In the present study, advanced fibrosis as determined by Hepascore or liver biopsy was present in 24 and 20.0% of MTX patients, respectively. An early report found a rate of 23.1% of advanced fibrosis in 104 patients,[4] whereas in more recent studies, rates ranged from 4%[21] to 8.2%.[10] In RA patients treated with MTX, 6.5% had cirrhosis, and 0.7% developed liver decompensation.[22,23] In our study, the higher rates of advanced fibrosis and cirrhosis may be due to the higher cumulative MTX dose and longer follow-up period.

Previous studies suggested that patients with psoriasis were more susceptible to MTX-induced hepatotoxicity compared to patients with RA.[24] This was postulated to be due to the increased risk of underlying NAFLD in psoriatic patients.[25] In contrast, another study that included 119 RA and 690 psoriasis patients found no difference in the risk of MTX-induced DILI.[26] Importantly, these previous studies only used LFT instead of

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Table 2 Risk factors associated with all-cause mortality

	Univariable	*P*	Multivariable	*P*
Age	1.07 (0.99–1.14)	0.062	—	—
Gender, female *versus* male	1.34 (0.30–6.05)	0.704	—	—
Hepascore ≥ 0.84	7.91 (1.52–41.29)	0.014	184.4 (5.71–5958.5)	0.003
Disease for MTX treatment, rheumatoid arthritis *vs* psoriasis	0.87 (0.29–2.66)	0.809	0.18 (0.03–1.01)	0.052
MTX cumulative dosage	0.97 (0.78–1.19)	0.742	—	
Ever stopped MTX due to liver reason yes/no	1.11 (0.21–5.74)	0.902	—	
Diabetes	0.71 (0.31–1.62)	0.416	—	
Hypertension	1.44 (0.32–6.47)	0.633	—	
Dyslipidemia	1.20 (0.27–5.36)	0.813	0.14 (0.02–1.43)	0.098
Number of liver diseases	1.04 (0.31–3.48)	0.953	—	
Taking steroids	0.76 (0.09–6.30)	0.798	0.09 (0.01–1.58)	0.099
Taking other DMARD	0.73 (0.09–6.11)	0.775	—	

Complete clinical data were available in a subgroup of 35 patients. Data were presented as hazard ratios and 95% confidence intervals. Cox regression was performed, and multivariate analysis was achieved by stepwise backward conditional selection.
MTX, methotrexate.

liver biopsy as the DILI criteria, which may explain the disparity in results. In the present study, no difference was found in the severity of liver biopsy fibrosis between psoriasis and RA. Therefore, the different susceptibilities to MTX toxicity between psoriasis and RA requires further study.

Conversely, a baseline Hepascore <0.84 accurately predicted the absence of liver cirrhosis and adverse long-term liver outcomes in those using long-term MTX. Moreover, no liver-related outcome was found in patients with a consistently lower Hepascore 12 months after baseline.

It has been previously shown that a Hepascore >0.5 was associated with a 32.8 times higher risk of liver-related mortality and a 6.7 times higher risk for all-cause mortality in chronic hepatitis C.[17] Other noninvasive serum markers have also been studied before. PIIINP had a 100% negative predictive value for predicting MTX-induced liver fibrosis in psoriasis patients[12]; however, it also had a high false positive rate.[14] The Enhanced Liver Fibrosis assay (ELF; composite marker of serum hyaluronic acid, PIIINP, and tissue inhibitor of metalloproteinase 1)[27] was demonstrated to have improved diagnostic accuracy compared with PIIINP for predicting liver fibrosis in 27 psoriasis patients treated with MTX.[28]

Interestingly, the present study demonstrated a significant association between Hepascore and all-cause mortality. The association between Hepascore and liver outcome did not account for this as LRD occurred only in two of nine deaths. Three of the nine deaths were due to infection, and a baseline Hepascore ≥0.84 was significantly associated with death due to infection (log-rank $P = 0.027$; data not shown). The liver plays an important role in the control of systemic infection, and underlying liver injury is an independent risk factor for adverse outcomes with infection.[29,30] It is possible that patients with liver injury due to long-term MTX use were more likely to develop severe systemic infections and death.

The limitations of this study are the potential selection bias resulting from the inclusion of only those patients using long-term MTX therapy and who had a Hepascore performed. Other limitations include lacking transient elastography assessment and only having complete drug and clinical information in a small number of patients. This precludes further subgroup analysis. Finally, the lack of lifestyle data, such as obesity and alcohol intake, prevents the identification of other important cofactors in liver fibrosis development. Hepascore values were elevated in active psoriasis,[31] and likewise, ELF was elevated in PsO, PsA, and RA compared to healthy controls.[32] However, no liver biopsy data were included in these studies. Hepascore values may be more accurate in predicting liver fibrosis when immunological disorders are stable and well controlled.

In conclusion, the risks of adverse liver-related clinical outcomes were relatively low in long-term MTX users in Australia. Hepascore values performed at baseline and after 12 months of therapy were able to accurately stratify the risk of adverse liver-related outcomes and all-cause mortality in this patient group. Hepascore monitoring in long-term MTX users may be a useful management tool to detect the progression of liver fibrosis. The association between increased Hepascore and all-cause mortality requires further investigation.

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