The UK-PBC Risk Scores: derivation and validation of a scoring system for long-term prediction of end-stage liver disease in primary biliary cirrhosis

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Abstract

**Background:** The biochemical response to ursodeoxycholic acid (UDCA) – so-called ‘treatment response’ – strongly predicts long-term outcome in primary biliary cirrhosis (PBC). Several long-term prognostic models based solely on the treatment response have been developed that are widely used to risk-stratify PBC patients and guide their management. However, they do not take other prognostic variables into account, such as the stage of the liver disease. We sought to improve existing long-term prognostic models of PBC using data from the UK-PBC Research Cohort. **Methods:** We performed Cox proportional hazards regression analysis of diverse explanatory variables in a derivation cohort of 1,916 UDCA-treated participants. We used non-automatic backward selection to derive the best-fitting Cox model, from which we derived a multivariable fractional polynomial (MFP) model. We combined linear predictors and baseline survivor functions in equations to score the risk of a liver transplant or liver-related death occurring within 5, 10 or 15 years. We validated these risk scores in an independent cohort of 1,249 UDCA-treated participants. **Results:** The best-fitting model consisted of the baseline albumin and platelet count, as well as the bilirubin, transaminases and alkaline phosphatase after 12 months of UDCA. In the validation cohort, the 5, 10 and 15-year risk scores were highly accurate (AUCs > 0.90). **Conclusions:** The prognosis of PBC patients can be accurately evaluated using the UK-PBC risk scores. They may be used to identify high-risk patients for closer monitoring and second-line therapies, as well as low-risk patients who could potentially be followed-up in primary care.
Primary biliary cirrhosis (PBC) is a chronic liver disease in which autoimmune destruction of the intrahepatic bile ducts results in cholestasis and progressive fibrosis (1). The biliary injury may eventually lead to cirrhosis and liver failure – but the rate of disease progression is variable (2). Across the spectrum, some patients with PBC progress to end-stage liver disease (ESLD) within a few years of diagnosis; some develop cirrhosis that remains well-compensated; others (perhaps the majority) do not even develop cirrhosis. In PBC, as in other conditions, accurate prognostication enables management of the disease to be tailored to the patient. This is the basis of precision medicine - and it has clear benefits: patients at higher risk of adverse outcomes may be prioritized for closer monitoring and second-line therapy; those at low risk may be reassured and followed-up less frequently, even in primary care. This enables better distribution of health-care resources, reducing costs and improving delivery (3).

The only licensed pharmacotherapy for PBC is ursodeoxycholic acid (UDCA). Treatment with UDCA has been shown to improve survival in PBC and for this reason, it is recommended that all patients with PBC take UDCA at a dose of 13 – 15 mg/kg/day (1, 4, 5). In 2006, it was shown that the biochemical response to treatment with UDCA – so-called ‘treatment response’ – strongly predicts long-term outcome in PBC (6). This was a major advance that prompted the development of several prognostic models based solely on treatment response, including the Barcelona, Paris I, Rotterdam, Toronto and Paris II criteria (6-10). These models are highly accurate – and used increasingly to risk-stratify PBC patients and guide their management (2). However, it was shown more recently that the aspartate transaminase (AST) to platelet ratio index also predicts outcomes in PBC, independent of UDCA response (11). This suggests that existing prognostic models of PBC might be improved by taking other variables into account.

In the current study, we aimed to incorporate measures of treatment response with other prognostic variables in a new, long-term prognostic model of PBC that could be used to estimate the absolute risk of developing ESLD within specific time points in the future. To do so, we analysed data
from a derivation cohort consisting of 1,916 UDCA-treated participants, selected at random from the UK-PBC Research Cohort. We derived a scoring system based on treatment response and markers of disease stage. We then validated the scoring system in an independent, validation cohort consisting of 1,249 UDCA-treated participants, also selected at random from the UK-PBC Research Cohort.

Methods

Study Design

We used data from PBC patients enrolled in the UK-PBC Research Cohort. The cohort has been described in detail elsewhere (in particular, see http://www.uk-pbc.com/about/aboutuk-pbc/ws1/researchcohort/ and Carbone et al., 2013) (2). Briefly, PBC was defined according to the guidelines of the European Association for the Study of Liver (EASL) (1). Participants included in the current study were (1) patients with PBC incident or prevalent between 1st January 2008 and 31st July 2014, or (2) LT recipients who had undergone LT for PBC at any point before 31st July 2014.

Participants were recruited throughout the UK via the UK-PBC Consortium, a research network of 155 National Health Service (NHS) Trusts or Health Boards collaborating in the UK-PBC project (http://www.uk-pbc.com/). Of note, the UK-PBC Consortium includes every hospital providing general or specialist hepatology services in Great Britain, as well as the only major liver treatment centre in Northern Ireland. In collaborating centres, PBC patients were identified (1) by searching outpatient clinic records for patients registered with a diagnosis of PBC or LT for PBC, and (2) by searching immunology laboratory databases for samples with a positive test for anti-mitochondrial antibody (AMA). Patients with a confirmed diagnosis of PBC or LT for PBC were invited to join the UK-PBC Research Cohort.

We retrospectively reviewed the medical records of all participants to obtain baseline clinical data and to ascertain events occurring before the date of recruitment. Participants who had not suffered an event prior to the date of recruitment were prospectively followed-up until 31st July 2014.
The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. All participants provided written informed consent. The study was approved by the Oxford C research ethics committee (REC reference 07/H0606/96) and by the Research and Development Department of each collaborating hospital.

**Data source**

Data were captured using baseline and follow-up case record forms (CRFs) that were completed by suitably trained research nurses in collaborating centres. The baseline CRF captured information on the date of diagnosis and the explanatory variables listed below. Follow-up CRFs captured information on survival status and the date and cause of death (if applicable); LT status and date of LT (if applicable); contemporaneous laboratory investigations, and ongoing treatment with UDCA.

The most recent follow-up CRF was sent to collaborating centres in July 2014.

For each participant, the baseline CRF was sent to the hospital where the participant first received a diagnosis of PBC, which might be different from the recruiting centre. Follow-up CRFs were sent to the participant’s current treatment centre, which might also be different to the recruiting centre. This was possible because all centres providing general or specialist liver services in Great Britain are collaborating in the study. This ensured that follow-up was complete for all participants.

Completed CRFs underwent quality control (QC) for completeness and accuracy at the University of Cambridge. Missing or inaccurate data were systematically queried with the participant or research nurse who completed the form. Data that passed QC were uploaded into a bespoke database.

**Study entry and outcome**

We calculated the time from the diagnosis of PBC to an event. The date of diagnosis of PBC was defined as the date of the first positive test for anti-mitochondrial antibody (AMA) or, for seronegative patients, the date of the diagnostic liver biopsy.
Events were defined to reflect ESLD requiring LT, as follows: (1) death from a liver-related cause, meaning liver failure, variceal haemorrhage or hepatocellular carcinoma (HCC); (2) LT for PBC, or (3) for participants who were still alive and had never undergone LT, serum bilirubin measuring ≥100μmol/L for the first time. We considered LT for PBC to be an acceptable surrogate for liver-related death, having confirmed that >90% of PBC LT recipients in the UK have biochemical evidence of liver failure at the time of transplantation, reflected by a United Kingdom model for End-stage Liver Disease (UKELD) score >49 (Personal communication, NHS Blood and Transfusion [NHSBT]; Supplementary Figure S1) (12). Furthermore, we selected the threshold, bilirubin ≥100μmol/L, because bilirubin at this level is widely accepted to be an indication for LT, as reported in the EASL guidelines on the management of cholestatic liver diseases, 2009 (1).

Participants who did not reach an event were censored at the date of their most recent blood tests or the date of non-liver related death, if applicable.

Explanatory variables

We considered variables for inclusion in the risk score that were clinically relevant or had been shown in at least one previous study to predict survival in PBC. These variables were as follows:

- Age at diagnosis;
- Sex;
- Year of diagnosis;
- Blood tests at the time of diagnosis, i.e. serum sodium, creatinine, bilirubin (BIL), alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), platelet count, prothrombin time (PT) and international normalized ratio (INR), IgG, immunoglobulin A (IgA), immunoglobulin M (IgM), antinuclear antibodies (ANA), anti-mitochondrial antibodies (AMA) and anti-smooth-muscle antibodies (SMA) [presence/absence];
- Spleen size and the presence of ascites by ultrasound scan at the time of diagnosis;
• Treatment with UDCA (yes or no);
• Liver biochemistry after 12 months of treatment with UDCA. i.e. BIL12, ALT12, AST12 and ALP12.

To account for inter-operator variability in the measurement of laboratory investigations, research nurses were asked to provide the reference range reported for each laboratory investigation, as well as the result and date of the test. In our analysis, the creatinine, BIL, ALT, AST, ALP and immunoglobulins were treated as multiples of their respective upper reference levels. The sodium, albumin and platelet count were treated as multiples of their respective lower reference levels.

Measurements for both AST and ALT were available for comparatively few subjects (n=586, 14.6%) reflecting variation in biochemistry laboratory practice across the UK. We therefore defined a variable, transaminases (TA) that was the ALT where this was available, otherwise the AST. Likewise, measurements for both PT and INR were available for comparatively few patients (n=897, 21.4%). Where the INR was missing, we estimated the INR to be the ratio of the PT to the mean normal prothrombin time, calculated as the mean of the upper and lower reference level in that hospital.

Treatment with UDCA was included as a dichotomous explanatory variable (i.e. any treatment or no treatment). We did not account for the baseline, weight-adjusted dose of UDCA because these data were not available. However, we identified a subgroup of participants for whom the current weight-adjusted dose of UDCA was available (n = 1,253). In this subgroup, the median dose of UDCA was 12 mg/kg/day (IQR 9 – 14 mg/kg/day). This is lower than the recommended dose of UDCA (13-15 mg/kg/day), albeit comparable to the median dose reported by Lammers et al. (13) in their study of 4,845 PBC patients from leading academic centres across the globe. Notably, we found that the vast majority of participants taking UDCA <13 mg/kg/day fulfilled the Paris I definition of treatment response, suggesting they were receiving an individually effective dose (Supplementary Figure S2). For this reason, we did not consider that failing to account for weight-adjusted dose of UDCA would substantially bias our analysis.
Derivation of PBC risk scores

For the derivation and the validation of the risk scores we excluded participants confirmed to have another chronic liver disease in addition to PBC. We also excluded participants with PBC-autoimmune hepatitis (AIH) overlap syndrome, defined as interface hepatitis on liver histology combined with TA≥5×ULN or IgG≥2×ULN, over-and-above features of PBC (14). Finally, we excluded participants who had never received UDCA; had received <12 months of treatment with UDCA, or had discontinued UDCA prematurely for any reason other than death or LT. This left a cohort of participants with pure PBC who had received ongoing treatment with UDCA for at least 12 months. Following convention (15, 16) we randomly allocated 60% of these UDCA-treated participants to a derivation cohort and the remaining 40% to a validation cohort.

Within the derivation cohort, we undertook multiple imputation using chained equations (20 imputations) to account for missing values; as well as the predictor variables, the imputation model also included the binary event/censoring variable and Nelson-Aalen estimate of cumulative hazard (17). We performed univariate analysis of 20 variables (listed in Table 1) using Cox proportional hazards regression. Variables that were statistically significant at $P = 0.05$ in univariate analysis were included in a multivariable Cox model. Non-automatic backward selection was employed to identify the best fitting model, adjusting for age and calendar year at diagnosis in each iteration of model reduction. The multivariable fractional polynomial (mfp) procedure in Stata was used to identify the most appropriate functional form for each of the variables included in the best-fitting model. The coefficients were combined with the baseline survivor functions estimated from the model to derive three separate equations predicting the risk of an event occurring within 5, 10 or 15 years of baseline, respectively. Hereafter we refer to these equations as the 5, 10 and 15-year risk scores.

Validation of the PBC risk score

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We applied the 5, 10 and 15-year risk scores to participants in the validation cohort. To assess discrimination, we calculated the area under receiver operating characteristic curve (AUC) for each risk score. To assess calibration, we compared the observed versus predicted risk of an event occurring within 5, 10 or 15 years across each decile of the 5, 10 and 15-year risk scores, respectively. For comparison, we also assessed the discrimination of the Paris 1, Barcelona, Paris 2 and Toronto models at 5, 10 and 15 years using the AUC.

To assess the accuracy of the risk scores for measurement of risk prior to treatment, we calculated the 5, 10 and 15-year risk scores in a group of participants who had never been established on UDCA and had been followed-up for at least 12 months, using the baseline BIL, TA and ALP instead of the equivalent measurements on treatment. We then calculated the respective AUCs. To assess the accuracy of the risk scores using the ALT12 rather than TA12, we calculated the 5, 10 and 15-year risk scores using the ALT12 for all participants in the validation cohort for whom this measurement was available. We then calculated the respective AUCs. Likewise, to assess the accuracy of the risk scores using the AST12 rather than TA12, we calculated each risk score using the AST12 for all participants in the validation cohort for whom this measurement was available, then calculated the respective AUCs.

All analyses were performed using Stata version 13.0 (StataCorp, Texas 77845 USA).

**Results**

**Cohort characteristics**

A total of 4099 patients with PBC were recruited to the cohort up to 31\textsuperscript{st} July 2015. Of these, 77 were confirmed to have PBC-AIH overlap syndrome or another liver disease in addition to PBC; these participants were excluded from further analysis. Of those remaining, we excluded 857 participants who had never received UDCA; had received <12 months of treatment with UDCA, or had
discontinued UDCA prematurely. This left 3165 UDCA-treated participants, whom we included in the analysis.

In these UDCA-treated participants, the year of diagnosis of PBC ranged from 1974-2014 (Supplementary Figure S3A). The year of diagnosis in those who had undergone LT also ranged from 1974-2014 (Supplementary Figure S3B). The median duration of follow-up was 6.3 years (interquartile range [IQR], 3.2 – 10.7 years) and the total follow up was 23,673 patient-years. During follow-up, 291 patients (9.2%) suffered an event: 260 patients (8.2%) underwent LT and 31 patients (1%) died from liver-related causes. The overall event-free survival rate was 96% at 5 years, 89% at 10 years and 86% at 15 years, comparable to other, recent series (7).

These UDCA-treated participants were randomly allocated to a derivation cohort consisting of 1,916 participants or validation cohort consisting of 1,249 participants. The baseline characteristics of participants in the derivation and validation cohorts are shown in Table 1; the cohorts were similar, as expected from random allocation. Consistent with other recent series (7, 18, 19), approximately 10% of participants had advanced disease at diagnosis (exemplified here by splenomegaly or ascites) and approximately 20% of participants were ANA positive. Complete information about explanatory variables was available for 1,460 participants (76%) in the derivation cohort and for 959 participants (77%) in the validation cohort. Information on outcome was available for all participants. The rate of missing information for each variable is shown in Supplementary Table S1.

**Derivation of a PBC risk score**

In univariate analysis, age at diagnosis, calendar year at diagnosis, Na, BIL, TA, ALP, albumin, platelets, IgG, ANA, splenomegaly, ascites, BIL12, ALP12 and TA12 were associated with outcome and were taken forward for multivariable modelling. Following non-automatic backward selection, the best fitting Cox model included five variables: albumin, platelet, BIL12, TA12 and ALP12, with a Harrell’s c statistic of 0.92 (Table 2). Each iteration of the multivariable model was adjusted for age.
and calendar year at diagnosis but these variables did not significantly improve the fit and were excluded from the final model (data not shown).

Figure 1 shows the relationship between the hazard ratio for an event and each variable within the final model, with the best-fitting polynomial lines that describe this relationship. Fractional polynomial terms, baseline survivor function at 5, 10 and 15 years and regression coefficients for the best-fitting fractional polynomial model were included in the scoring system as follows:

**UK-PBC Risk Scores =**

\[ 1 \text{-baseline survival function}^\exp(0.0287854\times(\text{alp12xuln-1.722136304})-0.0422873\times((\text{altast12xuln/10})^1-8.675729006)+1.4199\times(\ln(\text{bil12xuln/10})+2.709607778)-1.960303\times(\text{albxlln-1.17673001})-.4161954\times(\text{pltxlln-1.873564875})) \]

*Note:* Baseline survivor function = 0.982 (at 5 years); 0.941 (at 10 years); 0.893 (at 15 years).

**Validation of the PBC risk score**

A total of 1,109 participants (89%) in the validation cohort had values for BIL12, TA12, ALP12, albumin and platelets, and were included in the validation analysis. One hundred and fourteen patients (9.1%) suffered an event during the follow-up.

In the validation cohort, the AUC was 0.96 (95% CI, 0.93-0.99) for the 5 year risk score; 0.95 (0.93-0.98) for the 10 year risk score, and 0.94 (0.91-0.97) for the 15 year risk score (Figure 2). In comparison, the AUCs of previous models for events within 5, 10 or 15 years were as follows: *Barcelona* = 0.56, 0.61, 0.61; *Paris I* = 0.81, 0.81, 0.80; *Toronto* = 0.65, 0.70, 0.70, and *Paris II* = 0.75, 0.75, 0.74, respectively (Figure 3). The predicted versus observed risk of an event across each decile of the 5, 10 and 15 year risk scores in shown in Figure 4. There is close correspondence between the predicted and observed risks, suggesting that the risk scores are well calibrated.
The ALT12 was available for 944 subject in the validation cohort, of whom 53 (5.6%) suffered an event during follow-up. The risk score using the ALT12 instead of TA12 had high discrimination in this subgroup, the AUC being 0.91 (0.86-0.95), 0.93 (0.90-0.97), and 0.91 (0.85-0.97) for the 5, 10, and 15 year risk scores, respectively. The AST12 was available for 376 subjects in the validation cohort, of whom 42 (11.2%) suffered an event during follow-up. The risk score using the AST12 instead of TA12 had high discrimination in this subgroup, the AUC being 0.86 (0.76-0.96), 0.90 (0.85-0.96), and 0.87 (0.80-0.93) for the 5, 10, and 15 year risk scores.

A total of 754 participants had never been established on UDCA and had been followed-up for at least 12 months. In this subgroup of untreated participants, the median follow-up was 6.65 years (IQR, 3.5 – 10.6 years); total follow-up was 5,646 patient-years, and 201 (26.7%) suffered an event. The risk scores applied to this subgroup using the baseline BIL, TA and ALP (instead of the equivalent measurements after 12 months of treatment) had high discrimination, the AUC being 0.96 (0.94-0.98), 0.94 (0.91-0.96) and 0.91 (0.88-0.94) for the 5, 10, and 15 year risk scores, respectively (Figure 5).

Discussion

We analysed data from more than 3,000 participants in the UK-PBC Research Cohort to develop and validate a scoring system for long-term prediction of ESLD. The scoring system incorporates readily available and objective laboratory measures, i.e. the baseline platelet count and serum albumin, and the serum bilirubin, transaminases and ALP measured after twelve months of treatment with UDCA. The scoring system is proposed to facilitate management of PBC in clinical practice.

In the current study, we confirmed that existing long-term prognostic models of PBC are accurate, with AUCs up to 0.81 for the Paris I model. However, the UK-PBC scoring system was superior to existing models, with AUCs of 0.96, 0.95 and 0.94 for the 5, 10 and 15 year risk scores, respectively. There are several reasons for its strong performance. The derivation cohort was sizeable, with 1,916
subjects and 177 events. The underlying model incorporated not only variables that define the treatment response (ALP12, TA12, and BIL12) but also crude measures of hepatic fibrosis (platelet count) and hepatocellular synthetic function (serum albumin). Continuous variables were treated as such; variables were transformed using multiple fractional polynomials, and the contribution of each variable to the prediction model was weighted according to its prognostic value.

A major advantage of our scoring system is that it provides accurate, individualised estimates of the risk of developing ESLD within defined time points in the future. This contrasts with existing long-term prognostic models that dichotomise patients into treatment responders or non-responders, at low or high risk of developing ESLD at an unknown point in the future (Supplementary Figure S4). In clinical practice, the scoring system should be most useful to identify patients who would obtain greatest benefit from further risk-reduction using second-line therapy. This is especially pertinent in PBC, with second-line agents currently in development (20). However, it should also be useful to identify patients at low risk of developing ESLD within a relevant time-frame, who could potentially be monitored in primary care.

Although the scoring system was derived primarily to evaluate long-term risk in PBC patients on treatment, we found that the risk scores achieved AUCs >0.90 in untreated participants. The scoring system should therefore provide accurate estimates of long-term risk prior to treatment – and then provide accurate re-evaluation of the long-term risk once treatment has been established. As such, the scoring system may be used to quantify risk-reduction and the treatment benefit derived from first-line therapy. However, our untreated validation cohort was comparatively small and this observation should be interpreted with care. To show readers how the scoring system might be applied in clinical practice, a calculator for the 5, 10 and 15 year risk scores is provided in the 

Supplementary Document. Furthermore, Supplementary Textbox 1 provides three examples of the scoring system used to guide the clinical management of hypothetical patients with PBC.
We anticipate that some clinicians may call for specific risk thresholds to simplify clinical decision-making. This is beyond the scope of the current study. There is no consensus in the literature on (a) how many risk groups should be created, and (b) where (and why) to position the cut-points. Developing sensible guidance for choosing risk groups remains a topic for further research (21).

Furthermore, we emphasise that risk must be contextualised. Consider a patient in whom the 15-year risk score is 20%. This level of risk would be unacceptable for a 35-year old with no comorbidities – but it might be acceptable for a 70-year old with another life-shortening disease. Treatment targets should therefore be determined by the cost-effectiveness of the treatment; its side-effect profile, and the extent to which the individual patient would benefit from the risk-reduction.

The UK-PBC Research Cohort consists of thousands of patients recruited from general as well as specialist centres across the entire UK. For this reason, we believe that the cohort is highly representative. The scoring system should therefore be widely applicable.

However, we acknowledge certain limitations. The model includes measurements at baseline and after 12 months of treatment. We do not anticipate a substantial change in the platelet count or serum albumin after 12 months of treatment with UDCA and for this reason, we consider all the measurements in the model to represent a single point in the course of the patient's disease. The strong fit of the final model in treated and untreated participants supports this assumption, although we did not specifically test the assumption in the current study. We are in the process of capturing additional data that will enable us to model liver-related outcomes using sets of variables measured at different time-points before and after starting treatment. These data will also enable us to develop of models incorporating repeated measurements. Participants in the UK-PBC Research Cohort may be taking a sub-optimal dose of UDCA. This could potentially bias the study, if UDCA has dose-dependent, beneficial effects over-and-above those measured by the liver biochemistry on treatment. However, survival rates in the UK-PBC Research Cohort were comparable to those of
cohorts in which patients received the optimal dose of UDCA. For this reason, if there is bias related to the dose of UDCA, it is likely to be minimal. In the current dataset, HCC and variceal haemorrhage have not been ascertained, except as a cause of death or indication for LT. It is therefore uncertain whether the scoring system accurately predicts HCC or variceal haemorrhage, per se. However, with additional data on these outcomes we will be able to specifically address these questions. The risk scores were derived using the variable TA instead of ALT or AST. However, we have shown that they perform equally well when just the ALT is used for TA, or just the AST. The underlying model uses the platelet count as a crude measure of disease stage. This is advantageous because the platelet count is readily available. However, more-accurate and dynamic measures of liver fibrosis such as transient elastography may be preferable. This would be especially true if anti-fibrotic therapies were available, when it would be important to quantify reduction in fibrosis.

In conclusion, we developed and validated the UK-PBC risk scores to assess the prognosis of patients with PBC using readily available and objective clinical measures. The scoring system has some advantages compared with previous prognostic models. Application of the scoring system in clinical practice may guide management and improve the distribution of health-care resources related to PBC. However, external validation of the scoring system in cohorts of treated and untreated patients is a pre-requisite to its application in clinical practice, and the scoring system should be updated as the size and characterization of the UK-PBC Research Cohort increases with time.
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AUTHOR CONTRIBUTIONS

Conceived and designed study: GFM, RNS, MC, DEJ, GJA, SJS, HJC

Supervised/coordinated data collection: GFM, MC, RNS, DP, SF, MAH, GMH, JMN, AKB, DT, AB, MA, CA, PT, KW, LG, RL

Performed or supervised laboratory work: GFM, MC, RNS

Performed statistical analyses: MC, SJS, GFM, HJC, NJW

Wrote first draft: MC, GFM, SJS

Commented critically and revised draft: all authors

The authors declare no competing financial interests.

URLs:

UK-PBC: http://www.uk-pbc.com/

Academic Department of Medical Genetics: http://medgen.medschl.cam.ac.uk/
Bibliography


Table 1. Characteristics of patients at baseline in the derivation and validation cohorts

<table>
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<th>Variables a, b</th>
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<th>Validation cohort (N=1249)</th>
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</tr>
<tr>
<td>Splenomegaly (&gt;12cm), n (%)</td>
<td>198 (10.3%)</td>
<td>97 (7.8%)</td>
<td>114 (15.1%)</td>
</tr>
<tr>
<td>Ascites, n (%)</td>
<td>22 (1.1%)</td>
<td>13 (1.0%)</td>
<td>20 (2.7%)</td>
</tr>
<tr>
<td>Na ratio</td>
<td>1.0 (1.0-1.1)</td>
<td>1.0 (1.0-1.0)</td>
<td>1.0 (1.0-1.1)</td>
</tr>
<tr>
<td>Creatinine ratio</td>
<td>0.7 (0.6-0.8)</td>
<td>0.7 (0.6-0.8)</td>
<td>0.7 (0.6-0.8)</td>
</tr>
<tr>
<td>BIL ratio</td>
<td>0.5 (0.4-0.8)</td>
<td>0.5 (0.4-0.8)</td>
<td>0.5 (0.4-0.9)</td>
</tr>
<tr>
<td>Albumin ratio</td>
<td>1.2 (1.1-1.3)</td>
<td>1.2 (1.1-1.3)</td>
<td>1.2 (1.1-1.3)</td>
</tr>
<tr>
<td>ALP ratio</td>
<td>1.9 (1.2-3.5)</td>
<td>2.1 (1.3-3.6)</td>
<td>1.5 (0.9-2.9)</td>
</tr>
<tr>
<td>TA ratio</td>
<td>1.4 (0.9-2.3)</td>
<td>1.4 (0.9-2.4)</td>
<td>1.2 (0.7-2.1)</td>
</tr>
<tr>
<td>Platelets ratio</td>
<td>1.8 (1.5-2.2)</td>
<td>1.8 (1.5-2.2)</td>
<td>1.8 (1.4-2.2)</td>
</tr>
<tr>
<td>INR</td>
<td>1.0 (0.9-1.0)</td>
<td>1.0 (0.9-1.0)</td>
<td>1.0 (0.9-1.1)</td>
</tr>
<tr>
<td>IgG ratio</td>
<td>0.9 (0.7-1.1)</td>
<td>0.9 (0.7-1.1)</td>
<td>0.9 (0.7-1.1)</td>
</tr>
<tr>
<td>BIL12 ratio</td>
<td>0.5 (0.4-0.7)</td>
<td>0.5 (0.4-0.7)</td>
<td>-</td>
</tr>
<tr>
<td>ALP12 ratio</td>
<td>1.2 (0.9-2.1)</td>
<td>1.3 (0.9-2.1)</td>
<td>-</td>
</tr>
<tr>
<td>TA12 ratio</td>
<td>0.8 (0.6-1.3)</td>
<td>0.8 (0.6-1.3)</td>
<td>-</td>
</tr>
<tr>
<td>Event rate</td>
<td>177 (9.2%)</td>
<td>114 (9.1%)</td>
<td>201 (26.7%)</td>
</tr>
</tbody>
</table>
To allow for inter-operator variability, the bilirubin, transaminases, ALP at baseline and after 12 months of UDCA, creatinine, INR and IgG were analysed as multiples of the upper reference level in the laboratories that measured them. The Na, albumin and platelet count were analysed as multiples of the lower reference level in the laboratories that measured them.

Values for all continuous variables are expressed as medians and IQRs.

This subgroup includes only participants who were not treated with UDCA and had been followed up for at least 12 months, in order to allow for a fair comparison with the other subgroups.

Abbreviations: AMA, anti-mitochondrial antibodies; ANA, anti-nuclear antibodies; ALP, alkaline phosphatase; ALP12, alkaline phosphatase after 12 months of UDCA; BIL12, bilirubin after 12 months of UDCA; IgG, immunoglobulin G; INR, international normalized ratio; LT, liver transplantation; n, number; SMA, anti-smooth muscle antibodies; TA12, transaminases after 12 months of UDCA.
Table 2. Cox regression analysis for liver event in the derivation cohort

<table>
<thead>
<tr>
<th></th>
<th>Univariate analyses</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95%CI</td>
<td>p Value</td>
<td>HR</td>
</tr>
<tr>
<td>Albumin ratio</td>
<td>0.007</td>
<td>0.002-0.020</td>
<td>&lt;0.001</td>
<td>0.052</td>
</tr>
<tr>
<td>Platelet ratio</td>
<td>0.336</td>
<td>0.247-0.457</td>
<td>&lt;0.001</td>
<td>0.362</td>
</tr>
<tr>
<td>BIL12 ratio</td>
<td>1.476</td>
<td>1.394-1.563</td>
<td>&lt;0.001</td>
<td>1.427</td>
</tr>
<tr>
<td>TA12 ratio</td>
<td>1.225</td>
<td>1.180-1.271</td>
<td>&lt;0.001</td>
<td>1.150</td>
</tr>
<tr>
<td>ALP12 ratio</td>
<td>1.275</td>
<td>1.216-1.337</td>
<td>&lt;0.001</td>
<td>1.103</td>
</tr>
<tr>
<td>Na ratio</td>
<td>0.001</td>
<td>0.001-0.002</td>
<td>&lt;0.001</td>
<td>-</td>
</tr>
<tr>
<td>Creatinine ratio</td>
<td>0.385</td>
<td>0.131-1.129</td>
<td>0.082</td>
<td>-</td>
</tr>
<tr>
<td>BIL ratio</td>
<td>1.178</td>
<td>1.148-1.208</td>
<td>&lt;0.001</td>
<td>-</td>
</tr>
<tr>
<td>ALP ratio</td>
<td>1.044</td>
<td>1.027-1.061</td>
<td>&lt;0.001</td>
<td>-</td>
</tr>
<tr>
<td>TA ratio</td>
<td>1.019</td>
<td>0.999-1.039</td>
<td>0.050</td>
<td>-</td>
</tr>
<tr>
<td>INR</td>
<td>1.420</td>
<td>0.839-2.401</td>
<td>0.191</td>
<td>-</td>
</tr>
<tr>
<td>IgG ratio</td>
<td>2.430</td>
<td>1.676-3.523</td>
<td>&lt;0.001</td>
<td>-</td>
</tr>
<tr>
<td>Age (year)</td>
<td>0.970</td>
<td>0.955-0.984</td>
<td>&lt;0.001</td>
<td>-</td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td>0.941</td>
<td>0.919-0.964</td>
<td>&lt;0.001</td>
<td>-</td>
</tr>
<tr>
<td>Female</td>
<td>0.816</td>
<td>0.443-1.503</td>
<td>0.514</td>
<td>-</td>
</tr>
<tr>
<td>ANA+</td>
<td>1.423</td>
<td>0.937-2.1</td>
<td>0.048</td>
<td>-</td>
</tr>
<tr>
<td>AMA+</td>
<td>1.090</td>
<td>0.589-2.020</td>
<td>0.782</td>
<td>-</td>
</tr>
<tr>
<td>SMA +</td>
<td>1.114</td>
<td>0.563-2.020</td>
<td>0.756</td>
<td>-</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>8.453</td>
<td>5.969-11.971</td>
<td>&lt;0.001</td>
<td>-</td>
</tr>
<tr>
<td>Ascites</td>
<td>11.732</td>
<td>6.283-21.905</td>
<td>&lt;0.001</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: AMA, anti-mitochondrial antibodies; ANA, anti-nuclear antibodies; ALP, alkaline phosphatase; ALP12, alkaline phosphatase after 12 months of UDCA; BIL12, bilirubin after 12 months of UDCA; IgG, immunoglobulin G; INR, international normalized ratio; LT, liver transplantation; n, number; SMA, anti-smooth muscle antibodies; TA12, transaminases after 12 months of UDCA; UDCA, ursodeoxycholic acid. Splenomegaly refers to a spleen length >12cm.
Figure 1. Relationship between the hazard ratio for a liver event (liver death or liver transplantation) and each variable within the final model together with the best-fitting polynomial line in the UK-PBC Research Cohort.

Relationship between the hazard ratio for a liver event and each variable included in the final model: (a) ALT; (b) Bili; (c) T4; (d) Albumin; (e) Malnutrition. To allow for inter-operator variability, Bili, T4, and ALT were analyzed as multiples of their upper reference levels whereas Albumin and Malnutrition were analyzed as multiples of their lower reference levels. The best-fitting polynomial lines to describe the relationship between risk and each variable is shown. Note in particular that for each variable, risk increases or decreases as a continuous and there are no points at which the trajectory of risk suddenly changes, which suggests that they are best modeled as continuous variables. Note also that some variables do not have a linear relationship with risk and for this reason, they were transformed using multivariable fractional polynomials (per test).

Abbreviations: ALT; alkaline phosphatase after 12 months of UDCA; Bili; bilirubin after 12 months of UDCA; T4; lower limit of normal; T4; TL4; transaminases after 12 months of UDCA; UN; upper limit of normal; UN; Urea; UN; uric acid; UN; Urea; UN; uric acid; UN.
Figure 2. Receiver operating characteristic (ROC) curves for the prediction of death or liver transplantation (LT) according to the UK-PBC risk scores at 5 (a), 10 (b) and 15 years (c).

Note: Area under the ROC curve (AUC) can be interpreted as a summary index of classification performance. An AUC value of 0.5 indicates a 'random call,' whereas an AUC value of 1.0 indicates perfect separation of events and non-events.

254x190mm (300 x 300 DPI)
Figure 3. Receiver operating characteristic (ROC) curves for the prediction of death or liver transplantation (LT) using the Barcelona, Paris I, Toronto and Paris II definitions of treatment response, in the UK-PBC cohort at 5 (a), 10 (b) and 20 years (c).

Each plot in Figure 3 shows only one point because the Barcelona, Paris I, Toronto and Paris II definitions of treatment response are dichotomous, having a cut-off threshold and only two states: responder and non-responder. The ROC curve is therefore plotted using the single, pre-determined thresholds. In contrast, the UK-PBC Five Scores are continuous. The ROC curve is therefore plotted by incrementally varying the threshold and measuring the area under the ROC curve. Comparison of the laboratory results was not possible because serum albumin after 12 months of treatment was not available for all participants in the cohort.

254x190mm (300 x 300 DPI)
Figure 4. Predicted versus observed risk of an event across each decile of the 5-year, 10-year and 15-year UK-PBC risk scores.

There is close correspondence between the predicted and observed risks, suggesting that the risk scores are well calibrated.

254x190mm (300 x 300 DPI)
Figure 5. Receiver-operator characteristic curves for the 5 (a), 10 (b) and 15 years (c) UK-PBC risk scores in the subgroup of untreated participants (n=754) of the UK-PBC cohort.

* This subgroup includes only participants who were not treated with UDCA and had been followed up for at least 1.2 months.

254x190mm (300 x 300 DPI)
The UK-PBC Risk Scores: derivation and validation of a scoring system to predict the long-term risk of end-stage liver disease in patients with PBC


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**Supplementary table S1.** Percentage of individuals with missing data for explanatory variables considered in the current study (N=3,165)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Missingness rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>0.4%</td>
</tr>
<tr>
<td>Sex</td>
<td>0.5%</td>
</tr>
<tr>
<td>LT</td>
<td>0.0%</td>
</tr>
<tr>
<td>ANA</td>
<td>22.3%</td>
</tr>
<tr>
<td>AMA</td>
<td>6.1%</td>
</tr>
<tr>
<td>SMA</td>
<td>17.8%</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>19.1%</td>
</tr>
<tr>
<td>Ascites</td>
<td>19.4%</td>
</tr>
<tr>
<td>Na</td>
<td>5.9%</td>
</tr>
<tr>
<td>Creatinine</td>
<td>6.3%</td>
</tr>
<tr>
<td>BIL</td>
<td>2.9%</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.8%</td>
</tr>
<tr>
<td>ALP</td>
<td>2.9%</td>
</tr>
<tr>
<td>TA</td>
<td>3.4%</td>
</tr>
<tr>
<td>Platelets</td>
<td>6.7%</td>
</tr>
<tr>
<td>INR</td>
<td>23.9%</td>
</tr>
<tr>
<td>IgG</td>
<td>33.4%</td>
</tr>
<tr>
<td>BIL12</td>
<td>10.3%</td>
</tr>
<tr>
<td>ALP12</td>
<td>11.3%</td>
</tr>
<tr>
<td>TA12</td>
<td>11.4%</td>
</tr>
</tbody>
</table>

*Abbreviations:* AMA, anti-mitochondrial antibodies; ANA, anti-nuclear antibodies; ALP, alkaline phosphatase; ALP12, alkaline phosphatase after 12 months of UDCA or at baseline for subjects not on UDCA; BIL12, bilirubin after 12 months of UDCA or at baseline for subjects not on UDCA; LT, liver transplantation; SMA, anti-smooth muscle antibodies; TA12, transaminases after 12 months of UDCA.
**Supplementary Figure S1:** Distribution of UKELD scores at time of liver transplantation in PBC LT recipients in the United Kingdom, 2008 – 2014.

The United Kingdom model for End-stage Liver Disease (UKELD) is a short-term prognostic model developed to predict death of patients with chronic liver disease on the waiting liver for liver transplantation (LT). Higher scores reflect increased risk. A score of 49 is accepted as an indication for LT. This histogram shows that in the time-frame 2008 – 2014, >92% of PBC LT recipients had a UKELD score ≥49 at the time of LT (n = 335). The median UKELD was 55. (Personal communication, NHS Blood and Transplant [NHSBT])
**Supplementary Figure S2.** Kernel density plots showing the distribution of the weight-based dose of ursodeoxycholic acid (UDCA) in a sub-group of participants in the UK-PBC Research Cohort (a) and the distribution of liver biochemistry measurements in these participants (b).

In the upper plot, the vertical line indicates the optimal dose of UDCA, 13 mg/kg/day. Note that the median dose of UDCA was approximately 12 mg/kg/day. In the lower plot, the vertical line represents 3xULN, which is the cut-off for ALP in the Paris I criteria for treatment response. Note that the vast majority of participants in this sub-group have achieved a good treatment response defined by the Paris I criteria, i.e. bilirubin ≤1xULN, ALT <2xULN and ALP<3xULN.
Supplementary Figure S3. Histogram showing the distribution of the year of diagnosis observed in the UK-PBC Research Cohort (a, N=3,165) and in the LT recipient subgroup (b, n=260) who received treatment with UDCA.
Supplementary Figure S4. Plot illustrating the major advantages of absolute risk evaluation using the UK-PBC Risk Scores over dichotomous risk stratification using the Paris I definition of treatment response.

The range of values for the 15-year risk score in Paris I non-responders (red circles) and Paris I responders (blue circles) in the current UK-PBC Research Cohort. Note that some “low-risk” responders have the same 15-year risk score as “high risk” non-responders. For example, the arrow points to Patient A, a “low-risk” responder whose estimated 15-year risk is >40%. This patient has near-normal bilirubin, ALT and ALP but her albumin is 28 and her platelet count is 87, reflecting splenomegaly of 16.5cm. The estimated absolute risk is therefore plausible. Note also that the estimated 15-year risk in non-responders ranges from <5% to 100%. Estimating the absolute risk may assist physicians with clinical decision making; it may also help patients to plan their futures.
**Supplementary Box S1.** Example of the application of the UK PBC risk scores to calculate the absolute risk of liver event in three different clinical scenarios

<table>
<thead>
<tr>
<th>Clinical case</th>
<th>UK-PBC risk score</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asymptomatic 75 year old patient with normal liver biochemistry (LFTs) on treatment, as shown below:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin=15 (normal range &lt;18)</td>
<td>2.8</td>
<td>9.2</td>
</tr>
<tr>
<td>Albumin=35 (30-45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALP=200 (&lt;130)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT=60 (&lt;50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count=240 (150-450)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5 year</strong></td>
<td>10 years</td>
<td>15 years</td>
</tr>
<tr>
<td>This patient has low risk of developing liver failure within five years and moderate risk within ten years. Considering the patient’s age, the physician might consider discharging the patient for follow-up in primary care.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>50 year old patient with early stage of liver disease but elevated LFTs on treatment, as shown below:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin=15 (normal range &lt;18)</td>
<td>3.6</td>
<td>11.4</td>
</tr>
<tr>
<td>Albumin=35 (30-45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALP=600 (&lt;130)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT=100 (&lt;50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count=240 (150-450)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5 year</strong></td>
<td>10 years</td>
<td>15 years</td>
</tr>
<tr>
<td>This patient has substantial risk of developing liver failure within 15 years owing to disease activity rather than disease stage. Considering the patient’s age, the physician might consider evaluating this patient for treatment with second-line agents.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>60 year old patient with advanced stage of liver disease but normal LFTs on treatment, as shown below:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin=30 (normal range &lt;18)</td>
<td>12.6</td>
<td>36.5</td>
</tr>
<tr>
<td>Albumin=28 (30-45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALP=100 (&lt;130)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT=40 (&lt;50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count=130 (150-450)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5 year</strong></td>
<td>10 years</td>
<td>15 years</td>
</tr>
<tr>
<td>This patient has substantial risk of developing liver failure within 5 years owing to advanced disease stage rather than disease activity. There would be little benefit from second-line agents. The physician might prioritise this patient for closer surveillance and assess for liver transplantation once the UKELD is ≥49 (or the equivalent).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
UK-PBC Consortium

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67. East Sussex Healthcare NHS Trust, Conquest Hospital, The Ridge, St Leonards-on-Sea TN37 7RD
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69. Epsom and St Helier University Hospitals NHS Trust, Epsom General Hospital, Epsom Hospital, Dorking Road, Epsom KT18 7EG
70. Frimley Health NHS Foundation Trust, Heatherwood Hospital, London Road, Ascot SL5 8AA
71. Frimley Health NHS Foundation Trust, Wexham Park Hospital, Slough SL2 4HL
72. Frimley Health NHS Foundation Trust, Frimley Park Hospital, Portsmouth Road, Frimley GU16 7UJ
73. Gateshead Health NHS Foundation Trust, Queen Elizabeth Hospital, Sheriff Hill, Gateshead NE9 6SX
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75. Gloucestershire Hospitals NHS Foundation Trust, Cheltenham General Hospital, Sandford Road, Cheltenham GL53 7AN
76. Gloucestershire Hospitals NHS Foundation Trust, Gloucestershire Royal Hospital, Great Western Road, Gloucester GL1 3NN
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78. Guy's and St Thomas' NHS Foundation Trust, St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH
79. Hampshire Hospitals NHS Foundation Trust, Royal Hampshire County Hospital, Romsey Road, Winchester SO22 5DG
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82. Heart of England NHS Foundation Trust, Good Hope Hospital, Rectory Road, Sutton Coldfield, Birmingham B75 7RR
83. Heart of England NHS Foundation Trust, Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS
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85. Hillingdon Hospitals NHS Foundation Trust, Hillingdon Hospital, Pield Heath Road, Uxbridge UB8 3NN
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87. Homerton University Hospital NHS Foundation Trust, Homerton University Hospital, Homerton Row, London E9 6SR
88. Hull And East Yorkshire Hospitals NHS Trust, Castle Hill Hospital, Castle Road, Cottingham HU16 5JQ
89. Hull And East Yorkshire Hospitals NHS Trust, Hull Royal Infirmary, Anlaby Road, Hull HU3 2JZ
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91. Hywel Dda University Health Board, Prince Philip Hospital, Bryngwyn Mawr, Dafen, Llanelli SA14 8QF
92. Hywel Dda University Health Board, Glanrhondda General Hospital, Dolgelli Road, Cwmbran NP44 2DD
93. Hywel Dda University Health Board, Bronygarth Hospital, Caradog Road, Aberystwyth SY23 1ER
94. Imperial College Healthcare NHS Trust, Charing Cross Hospital, Fulham Palace Road, London W6 8RF
95. Imperial College Healthcare NHS Trust, Hammersmith Hospital, Du Cane Road, London W12 0HS
96. Imperial College Healthcare NHS Trust, St Mary's Hospital, Praed Street, London W2 1NY
97. Ipswich Hospital NHS Trust, Ipswich Hospital, Heath Road, Ipswich IP4 5PD
98. Isle of Wight NHS Trust, St Mary's Hospital, Parkhurst Road, Newport PO30 5TG
99. James Paget University Hospitals NHS Foundation Trust, James Paget Hospital, Lowestoft Road, Gorleston, Great Yarmouth NR31 6LA
100. Kettering General Hospital NHS Foundation Trust, Kettering General Hospital, Rothwell Road, Kettering NN16 8UZ
101. Kings College Hospital NHS Foundation Trust, King's College Hospital, Denmark Hill, London SE5 9RS
102. King's College Hospital NHS Foundation Trust, Beckenham Royal Hospital, 395 Croydon Road, Beckenham BR3 3QL
103. King's College Hospital NHS Foundation Trust, Princess Royal University Hospital, Farnborough Common, Orpington BR6 8ND
104. Kingston Hospital NHS Foundation Trust, Kingston Hospital, Galsworthy Road, Kingston upon Thames KT2 7QB
105. Lancashire Teaching Hospitals NHS Foundation Trust, Chorley and South Ribble Hospital, Preston Road, Chorley PR7 1PP
106. Lancashire Teaching Hospitals NHS Foundation Trust, Royal Preston Hospital, Sharoe Green Lane North, Preston PR2 9HT
107. Leeds Teaching Hospitals NHS Trust, Leeds General Infirmary, Great George Street, Leeds LS1 3EX
108. Leeds Teaching Hospitals NHS Trust, St James's University Hospital, Beckett Street, Leeds LS9 7TF
109. Lewisham and Greenwich NHS Trust, The Queen Elizabeth, Woolwich, Stadium Road, Greenwich SE18 4QH
110. Lewisham and Greenwich NHS Trust, Lewisham Hospital, High Street, Lewisham SE13 6LH
111. London North West Healthcare NHS Trust, Central Middlesex Hospital, Acton Lane, Park Royal, London NW10 7NS
112. London North West Healthcare NHS Trust, Northwick Park and St Mark's Hospitals, Watford Road, Harrow HA1 3UJ
113. Luton and Dunstable University Hospital NHS Foundation Trust, Luton and Dunstable University Hospital, Lewsey Road, Luton LU4 0DZ
114. Maidstone and Tunbridge Wells NHS Trust, Maidstone Hospital, Hermitage Lane, Maidstone ME16 9QQ
115. Maidstone and Tunbridge Wells NHS Trust, Tunbridge Wells Hospital, Tonbridge Road, Pembury, Tunbridge Wells TN2 4QJ
116. Medway NHS Foundation Trust, Medway Maritime Hospital, Windmill Road, Gillingham ME7 5NY
117. Mid Cheshire Hospitals NHS Foundation Trust, Leighton Hospital, Middlewich Road, CW1 4QJ
118. Mid Essex Hospital Services NHS Trust, Broomfield Hospital, Court Road, Chelmsford CM1 7ET
119. Mid Essex Hospital Services NHS Trust, St Peters Hospital, Spital Road, Maldon CM9 6EG
120. Mid Yorkshire Hospitals NHS Trust, Dewsbury and District Hospital, Halifax Road, Dewsbury WF13 4HS
121. Milton Keynes Hospital NHS Foundation Trust, Milton Keynes Hospital, Standing Way, Milton Keynes MK6 5LD
122. Newcastle upon Tyne Hospitals NHS Foundation Trust, Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne NE7 7DN
123. NHS Ayrshire & Arran, University Hospital Crosshouse, Kilmarnock Road, Kilmarnock KA2 0BE
124. NHS Borders, Borders General Hospital, Melrose TD6 9BS
125. NHS Dumfries & Galloway, Dumfries and Galloway Royal Infirmary, Bankend Road, Dumfries DG1 4AP
126. NHS Fife, Queen Margaret Hospital, Whitefield Road, Dunfermline KY12 0SU
127. NHS Fife, Victoria Hospital, Hayfield Road, Kirkcaldy KY2 5AH
128. NHS Forth Valley, Forth Valley Royal Hospital, Stirling Road, Larbert FK5 4WR
129. NHS Forth Valley, Stirling Community Hospital, Livilands, Stirling FK8 2AU
130. NHS Grampian, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZN
131. NHS Grampian, Dr Gray's Hospital, Elgin IV30 1SN
132. NHS Grampian, Woolmanhill Hospital, Skene Street, Aberdeen AB25 1LD
133. NHS Greater Glasgow and Clyde, Gartnavel General Hospital, 1053 Great Western Road, Glasgow G12 0YN
134. NHS Greater Glasgow and Clyde, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF
135. NHS Greater Glasgow and Clyde, Inverclyde Royal Hospital, Larkfield Road, Greenock PA16 0XN
136. NHS Greater Glasgow and Clyde, Royal Alexandria Hospital, Corsebar Road, Paisley PA2 9PN
137. NHS Greater Glasgow and Clyde, Southern General Hospital, 1345 Govan Road, Glasgow G51 4TF
138. NHS Greater Glasgow and Clyde, Victoria Infirmary, Langside Road, Glasgow G42 9TY
139. NHS Highland, Caithness General Hospital, Bankhead Road, Wick KW1 5NS
140. NHS Highland, Raigmore Hospital, Old Perth Road, Inverness IV2 3UJ
141. NHS Lanarkshire, Hairmyres Hospital, Eaglesham Road, East Kilbride G75 7RG
142. NHS Lanarkshire, Monklands Hospital, Monkscourt Avenue, Airdrie ML6 0JS
143. NHS Lanarkshire, Wishaw General Hospital, 50 Netherton Street, Wishaw ML2 0DP
144. NHS Lothian, Royal Infirmary of Edinburgh, 51 Little France Crescent, Old Dalkeith Road, Edinburgh EH16 4SA
145. NHS Lothian, St John's Hospital, Howden Road West, Howden, Livingston EH54 6PP
146. NHS Lothian, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU
147. NHS Tayside, Perth Royal Infirmary, Taymount Terrace, Perth PH1 1NX
148. NHS Tayside, Ninewells Hospital, Dundee DD1 9SY
149. Norfolk and Norwich University Hospitals NHS Foundation Trust, Norfolk and Norwich University Hospital, Colney Lane, Norwich NR4 7UY
150. North Bristol NHS Trust, Frenchay Hospital, Frenchay Park Road, Bristol BS16 1LE
151. North Cumbria University Hospitals NHS Foundation Trust, Cumberland Infirmary, Newtown Road, Carlisle CA2 7HY
152. North Cumbria University Hospitals NHS Foundation Trust, West Cumberland Hospital, Hensingham, Whitehaven CA28 8JG
153. North Tees and Hartlepool NHS Foundation Trust, University Hospital of Hartlepool, Holdforth Road, Hartlepool TS24 9AH
154. North Tees and Hartlepool NHS Foundation Trust, University Hospital of North Tees, Hardwick, Stockton on Tees TS19 8PE
155. Northampton General Hospital NHS Trust, Northampton General Hospital, Cliftonville, Northampton NN1 5BD
156. Northern Devon Healthcare NHS Trust, North Devon District Hospital, Raleigh Park, Barnstaple EX31 4JB
157. Northern Health and Social Care Trust, Whiteabbey Hospital, Doagh Road, Newtownabbey BT37 9RH
158. Northern Lincolnshire and Goole NHS Foundation Trust, Diana, Princess of Wales Hospital, Scartho Road, Grimsby DN33 2BA
159. Northern Lincolnshire and Goole NHS Foundation Trust, Goole and District Hospital, Woodland Avenue, Goole DN14 6RX
160. Northern Lincolnshire and Goole NHS Foundation Trust, Scunthorpe General Hospital, Cliff Gardens, Scunthorpe DN15 7BH
161. Northumbria Healthcare NHS Foundation Trust, Hexham General Hospital, Corbridge Road, Hexham NE46 1QJ
162. Northumbria Healthcare NHS Foundation Trust, North Tyneside Hospital, Rake Lane, North Shields NE29 8NH
163. Nottingham University Hospitals NHS Trust, Nottingham City Hospital, Hucknall Road, Nottingham NG5 1PB
164. Nottingham University Hospitals NHS Trust, Queen’s Medical Centre, Derby Road, Nottingham NG7 2UH
165. Oxford University Hospitals NHS Trust, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU
166. Oxleas NHS Foundation Trust, Queen Mary’s Hospital Sidcup, Frogнал Avenue, Sidcup DA14 6LT
167. Pennine Acute Hospitals NHS Trust, Fairfield General Hospital, Rochdale Old Road, Bury BL9 7TD
168. Pennine Acute Hospitals NHS Trust, North Manchester General Hospital, Delaunays Road, Crumpsall M8 5RB
169. Pennine Acute Hospitals NHS Trust, Rochdale Infirmary, Whitehall Street, Rochdale OL12 0NB
170. Pennine Acute Hospitals NHS Trust, The Royal Oldham Hospital, Rochdale Road, Oldham OL1 2JH
171. Peterborough and Stamford Hospitals NHS Foundation Trust, Peterborough City Hospital, Edith Cavell Campus, Bretton Gate, Peterborough PE3 9GZ
172. Peterborough and Stamford Hospitals NHS Foundation Trust, Stamford & Rutland Hospital, Ryhall Road, Stamford PE9 1UA
173. Plymouth Hospitals NHS Trust, Derriford Hospital, Derriford Road, Plymouth PL6 8DH
174. Poole Hospital NHS Foundation Trust, Poole Hospital, Longfleet Road, Poole BH15 2JB
175. Portsmouth Hospitals NHS Trust, Queen Alexandra Hospital, Cosham, Portsmouth PO6 3LY
176. Princess Alexandra Hospital NHS Trust, St Margaret’s Hospital, The Plain, Epping CM16 6TN
177. Princess Alexandra Hospital NHS Trust, The Princess Alexandra Hospital, Harlow CM20 1X
178. Queen Elizabeth Hospital King’s Lynn NHS Foundation Trust, The Queen Elizabeth Hospital King’s Lynn, Gayton Road, King’s Lynn PE30 4ET
179. Rotherham NHS Foundation Trust, Rotherham Hospital, Moorgate Road, Rotherham S60 2UD
180. Royal Berkshire NHS Foundation Trust, Royal Berkshire Hospital, Craven Road, Reading RG1 5AN
181. Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust, Royal Bournemouth Hospital, Castle Lane East, Bournemouth BH7 7DW
182. Royal Cornwall Hospitals NHS Trust, Royal Cornwall Hospital, Treliske, Truro TR1 3LJ
183. Royal Devon and Exeter NHS Foundation Trust, Royal Devon and Exeter Hospital, Barrack Road, Exeter EX2 5DW
184. Royal Free London NHS Foundation Trust, The Royal Free Hospital, Pond Street, London NW3 2QG
185. Royal Free London NHS Foundation Trust, Barnet Hospital, Wellhouse Lane, Barnet EN5 3DJ
186. Royal Free London NHS Foundation Trust, Chase Farm Hospital, The Ridgeway, Enfield EN2 8JL
187. Royal Liverpool and Broadgreen University Hospitals NHS Trust, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP
188. Royal United Hospitals Bath NHS Foundation Trust, Royal United Bath Hospital, Combe Park, Bath BA1 3NG
189. Royal Wolverhampton Hospitals NHS Trust, New Cross Hospital, Wolverhampton Road, Wolverhampton WV10 0QP
190. Royal Wolverhampton Hospitals NHS Trust, Cannock Chase Hospital, Brunswick Road, Cannock WS11 5XY
191. Salisbury NHS Foundation Trust, Salisbury District Hospital, Salisbury SP2 8BJ
192. Sandwell and West Birmingham Hospitals NHS Trust, Sandwell General Hospital, Lyndon, West Bromwich B71 4HJ
193. Sheffield Teaching Hospitals NHS Foundation Trust, Northern General Hospital, Herries Road, Sheffield S5 7AU
194. Sheffield Teaching Hospitals NHS Foundation Trust, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF
195. Sherwood Forest Hospitals NHS Foundation Trust, King's Mill Hospital, Mansfield Road, Sutton in Ashfield NG17 4JL
196. Sherwood Forest Hospitals NHS Foundation Trust, Newark Hospital, Boundary Road, Newark NG24 4DE
197. Shrewsbury and Telford Hospital NHS Trust, Princess Royal Hospital, Apley Castle, Telford TF1 6TF
198. Shrewsbury and Telford Hospital NHS Trust, Royal Shrewsbury Hospital, Mytton Oak Road, Shrewsbury SY3 8QX
199. South Devon Healthcare NHS Foundation Trust, Torbay Hospital, Lowes Bridge, Torquay TQ2 7AA
200. South Eastern Health and Social Care Trust, Lagan Valley Hospital, 39 Hillsborough Road, Lisburn BT28 1JP
201. South Eastern Health and Social Care Trust, Ulster Hospital, Upper Newtownards Road, Dundonald, Belfast BT16 1RH
202. South Tees Hospitals NHS Foundation Trust, The James Cook University Hospital, Marton Road, Middlesbrough TS4 3BW
203. South Tees Hospitals NHS Foundation Trust, Friarage Hospital, Northallerton DL6 1JG
204. South Tyneside NHS Foundation Trust, South Tyneside District Hospital, Harton Lane, South Shields NE34 0PL
205. South Warwickshire NHS Foundation Trust, Warwick Hospital, Lakin Road, Warwick CV34 5BW
206. Southend University Hospital NHS Foundation Trust, Southend Hospital, Prittlewell Chase, Westcliff-on-Sea SS0 0RY
207. Southport & Ormskirk Hospital NHS Trust, Ormskirk District General Hospital, Wigan Road, Ormskirk L39 2AZ
208. Southport & Ormskirk Hospital NHS Trust, Southport and Formby District General Hospital, Town Lane, Kew, Southport PR8 6PN
209. St George's University Hospitals NHS Foundation Trust, St George's Hospital, Blackshaw Road, Tooting, London SW17 0QT
210. St Helens and Knowsley Teaching Hospitals NHS Trust, St Helens Hospital, Marshalls Cross Road, St Helens WA9 3DA
211. St Helens and Knowsley Teaching Hospitals NHS Trust, Whiston Hospital, Warrington Road, Prescot L35 5DR
212. Stockport NHS Foundation Trust, Stepping Hill Hospital, Poplar Grove, Hazel Grove, Stockport SK2 7JE
213. Surrey and Sussex Healthcare NHS Trust, East Surrey Hospital, Canada Avenue, Redhill RH1 5RH
214. Tameside General Hospital NHS Foundation Trust, Tameside General Hospital, Fountain Street, Ashton-under-Lyne OL6 9RW
215. United Lincolnshire Hospitals NHS Trust, Lincoln County Hospital, Greetwell Road, Lincoln LN2 5QY
216. United Lincolnshire Hospitals NHS Trust, Grantham and District Hospital, 101 Manthorpe Road, Grantham NG31 8DG
217. United Lincolnshire Hospitals NHS Trust, Pilgrim Hospital Boston, Sibsey Road, Boston PE21 9QS
218. University College London Hospitals NHS Foundation Trust, University College Hospital, 235 Euston Road, London NW1 2BU
219. University Hospital of South Manchester NHS Foundation Trust, Wythenshawe Hospital, Southmoor Road, Wythenshawe, Manchester M23 9LT
220. University Hospital Southampton NHS Foundation Trust, Southampton General Hospital, Tremona Road, Southampton SO16 6YD
221. University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Mindelsohn Way, Edgbaston, Birmingham B15 2GW
222. University Hospitals Bristol NHS Foundation Trust, Bristol Royal Infirmary, Upper Maudlin Street, Bristol BS2 8HW
223. University Hospitals Coventry and Warwickshire NHS Trust, University Hospital, Clifford Bridge Road, Coventry CV2 2DX
224. University Hospitals of Leicester NHS Trust, Glenfield Hospital, Groby Road, Leicester LE3 9QP
225. University Hospitals of Leicester NHS Trust, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW
226. University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary, Infirmary Square, Leicester LE1 5WW
227. University Hospitals of Morecambe Bay NHS Foundation Trust, Royal Lancaster Infirmary, Ashton Road, Lancaster LA1 4RP
228. University Hospitals of North Midlands NHS Trust, Royal Stoke University Hospital, Newcastle Road, Stoke-on-Trent ST4 6QG
229. University Hospitals of North Midlands NHS Trust, County Hospital, Weston Road, Stafford ST16 3SA
230. Walsall Healthcare NHS Trust, Walsall Manor Hospital, Moat Road, Walsall WS2 9PS
231. Warrington and Halton Hospitals NHS Foundation Trust, Warrington Hospital, Lovely Lane, Warrington WA5 1QG
232. West Hertfordshire Hospitals NHS Trust, Hemel Hempstead General Hospital, Hillfield Road, Hemel Hempstead HP2 4AD
233. West Hertfordshire Hospitals NHS Trust, St Albans City Hospital, Waverley Road, St Albans AL3 5PN
234. West Hertfordshire Hospitals NHS Trust, Watford General Hospital, Vicarage Road, Watford WD18 0HB
235. West Middlesex University NHS Trust, West Middlesex University Hospital, Twickenham Road, Isleworth TW7 6AF
236. West Suffolk NHS Foundation Trust, Walnut Tree Hospital, Walnut Tree Lane, Sudbury CO10 1BE
237. West Suffolk NHS Foundation Trust, West Suffolk Hospital, Hardwick Lane, Bury St Edmunds IP33 2QZ
238. Western Sussex Hospitals NHS Foundation Trust, Worthing Hospital, Lyndhurst Road, Worthing BN11 2DH
239. Western Sussex Hospitals NHS Foundation Trust, St Richard's Hospital, Spitalfield Lane, Chichester PO19 6SE
240. Weston Area Health NHS Trust, Weston General Hospital, Grange Road, Uphill, Weston super Mare BS23 4TQ
241. Whittington Hospital NHS Trust, The Whittington Hospital, Magdala Avenue, London N19 5NF
242. Wirral University Teaching Hospital NHS Foundation Trust, Arrowe Park Hospital, Upton CH49 5PE
243. Wirral University Teaching Hospital NHS Foundation Trust, Victoria Central Hospital, Mill Lane, Wallasey CH44 5UF
244. Worcestershire Acute Hospitals NHS Trust, Alexandra Hospital, Woodrow Drive, Redditch B98 7UB
245. Worcestershire Acute Hospitals NHS Trust, Kidderminster Hospital and Treatment Centre, Bewdley Road, Kidderminster DY11 6RJ
246. Worcestershire Acute Hospitals NHS Trust, Worcestershire Royal Hospital, Charles Hastings Way, Worcester WR5 1DD
247. Wrightington, Wigan And Leigh NHS Trust, Royal Albert Edward Infirmary, Wigan Lane, Wigan WN1 2NN
248. Wye Valley NHS Trust, The County Hospital, Stonebow Road, Hereford HR1 2BN
249. Yeovil District Hospital NHS Foundation Trust, Yeovil District Hospital, Higher Kingston, Yeovil BA21 4AT
250. York Teaching Hospital NHS Foundation Trust, Bridlington Hospital, Bessingby Road, Bridlington YO16 4QP
251. York Teaching Hospital NHS Foundation Trust, Scarborough Hospital, Woodlands Drive, Scarborough YO12 6QL
252. York Teaching Hospital NHS Foundation Trust, The York Hospital, Wigginton Road, York YO31 8HE
253. Great Western Hospitals NHS Foundation Trust, Marlborough Road, Swindon, Wiltshire SN3 6BB