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1. Abertawe Bro Morgannwg University Health Board, Morriston. Abertawe Bro Morgannwg University Health Board, Morriston Hospital, Heol Maes Eglwys, Morriston, Swansea SA6 6NL

2. Abertawe Bro Morgannwg University Health Board, Singleton Hospital, Sketty Lane, Sketty, Swansea SA2 8QA

3. Abertawe Bro Morgannwg University Health Board, Neath Port Talbot Hospital, Baglan Way, Port Talbot SA12 7BX

4. Abertawe Bro Morgannwg University Health Board, Princess of Wales Hospital, Coity Road, Bridgend CF31 1RQ

5. Aintree University Hospitals NHS Foundation Trust, Aintree University Hospital, Longmoor Lane, Liverpool L9 7AL

6. Airedale NHS Foundation Trust, Airedale General Hospital, Skipton Road, Steeton, Keighley BD20 6TD

7. Aneurin Bevan University Health Board, Nevill Hall Hospital, Brecon Road, Abergavenny NP7 7EG

8. Aneurin Bevan University Health Board, Royal Gwent Hospital, Cardiff Road, Newport NP20 2UB

9. Aneurin Bevan University Health Board, Ysbyty Ystrad Fawr, Ystrad Fawr Way, Ystrad Mynach, Hengoed CF82 7EP

10. Ashford & St Peter's Hospitals NHS Foundation Trust, Ashford Hospital, London Road, Ashford TW15 3AA

11. Ashford & St Peter's Hospitals NHS Foundation Trust, St Peter's Hospital, Guildford Road, Chertsey KT16 0PZ

12. Barking, Havering and Redbridge University Hospitals NHS Trust, King George Hospital, Barley Lane, Ilford IG3 8YB

13. Barking, Havering and Redbridge University Hospitals NHS Trust, Queen's Hospital, Rom Valley Way, Romford RM7 0AG

14. Barnsley Hospital NHS Foundation Trust, Barnsley Hospital, Gawber Road, Barnsley S75 2EP

15. Barts Health NHS Trust, The Royal London Hospital, Whitechapel Road, Whitechapel, London E1 1BB

16. Barts Health NHS Trust, Whipps Cross University Hospital, Whipps Cross Road, Leytonstone, London E11 1NR

17. Barts Health NHS Trust, Newham University Hospital, Glen Road, Plaistow, London E13 8SL

18. Basildon and Thurrock University Hospitals NHS Foundation Trust, Basildon University Hospital, Nethermayne, Basildon SS16 5NL

19. Bedford Hospital NHS Trust, Bedford Hospital, Kempston Road, Bedford MK42 9DJ

20. Belfast Health and Social Care Trust, Royal Victoria Hospital, 274 Grosvenor Road, Belfast BT12 6BA

21. Betsi Cadwaladr University Health Board, Glan Clwyd Hospital, Rhyl LL18 5UJ

22. Betsi Cadwaladr University Health Board, Ysbyty Gwynedd, Penrhosgarnedd, Bangor LL57 2PW

23. Betsi Cadwaladr University Health Board, Llandudno General Hospital, Hospital Road, Llandudno LL30 1LB

24. Betsi Cadwaladr University Health Board, Wrexham Maelor Hospital, Croesnewydd Road, Wrexham LL13 7TD

25. Blackpool Teaching Hospitals NHS Foundation Trusts, Blackpool Victoria Hospital, Whinney Heys Road, Blackpool FY3 8NR

26. Bolton NHS Foundation Trust, Royal Bolton Hospital, Minerva Road, Farnworth, Bolton BL4 0JR

27. Bradford Teaching Hospitals NHS Foundation Trust, Bradford Royal Infirmary, Duckworth Lane, Bradford BD9 6RJ

28. Brighton and Sussex University Hospitals NHS Trust, Princess Royal Hospital, Lewes Road, Haywards Heath RH16 4EX

29. Brighton and Sussex University Hospitals NHS Trust, Royal Sussex County Hospital, Eastern Road, Brighton BN2 5BE

30. Buckinghamshire Healthcare NHS Trust, Amersham Hospital, Whielden Street, Amersham HP7 0JD

31. Buckinghamshire Healthcare NHS Trust, Stoke Mandeville Hospital, Mandeville Road, Aylesbury HP21 8AL

32. Buckinghamshire Healthcare NHS Trust, Wycombe Hospital, Queen Alexandra Road, High Wycombe HP11 2TT

33. Burton Hospitals NHS Foundation Trust, Queen's Hospital, Belvedere Road, Burton upon Trent DE13 0RB

34. Calderdale And Huddersfield NHS Foundation Trust, Calderdale Royal Hospital, Salterhebble, Halifax HX3 0PW

35. Calderdale And Huddersfield NHS Foundation Trust, Huddersfield Royal Infirmary, Acre Street, Lindley, Huddersfield HD3 3EA

36. Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge Bio-medical Campus, Hills Road, Cambridge CB2 0QQ

37. Cardiff and Vale University Health Board, University Hospital Llandough, Penlan Road, Llandough, Penarth CF64 2XX

38. Cardiff and Vale University Health Board, University Hospital of Wales, Heath Park, Cardiff CF14 4XW

39. Central Manchester University Hospitals NHS Foundation Trust, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL

40. Chelsea and Westminster Hospital NHS Foundation Trust, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH

41. Chesterfield Royal Hospital NHS Foundation Trust, Chesterfield Royal Hospital, Calow, Chesterfield S44 5BL

42. City Hospitals Sunderland NHS Foundation Trust, Sunderland Royal Hospital, Kayll Road, Sunderland SR4 7TP

43. Colchester Hospital University NHS Foundation Trust, Colchester General Hospital, Turner Road, Colchester CO4 5JL

44. Countess of Chester Hospital NHS Foundation Trust, Countess of Chester Hospital, Countess of Chester Health Park, Liverpool Road, Chester CH2 1UL

45. County Durham and Darlington NHS Foundation Trust, Darlington Memorial Hospital, Hollyhurst Road, Darlington DL3 6HX

46. County Durham and Darlington NHS Foundation Trust, University Hospital of North Durham, North Road, Durham DH1 5TW

47. Croydon Health Services NHS Trust, Croydon University Hospital, 530 London Road, Croydon CR7 7YE

48. Croydon Health Services NHS Trust, Purley War Memorial Hospital, 856 Brighton Road, Purley CR8 2YL

49. Cwm Taf University Health Board, Prince Charles Hospital, Gurnos, Merthyr Tydfil CF47 9DT

50. Cwm Taf University Health Board, Royal Glamorgan Hospital, Ynysmaerdy, Llantrisant, Pontyclun CF72 8XR

51. Cwm Taf University Health Board, Ysbyty Cwm Cynon, New Road, Mountain Ash, Rhondda Cynon Taff CF45 4BZ

52. Dartford And Gravesham NHS Trust, Darent Valley Hospital, Darenth Wood Road, Dartford DA2 8DA

53. Derby Hospitals NHS Foundation Trust, Royal Derby Hospital, Uttoxeter Road, Derby DE22 3NE

54. Doncaster and Bassetlaw Hospitals NHS Foundation Trust, Bassetlaw Hospital, Blyth Road, Worksop S81 0BD

55. Doncaster and Bassetlaw Hospitals NHS Foundation Trust, Doncaster Royal Infirmary, Armthorpe Road, Doncaster DN2 5LT

# System for Long-Term Prediction of End-Stage Liver Disease in

56. Dorset County Hospitals NHS Foundation Trust, Dorset County Hospital, Williams Avenue, Dorchester DT1 2JY

57. Dudley Group of Hospitals NHS Trust, Russells Hall Hospital, Pensnett Road, Dudley DY1 2HQ

58. East and North Hertfordshire NHS Trust, Lister Hospital, Coreys Mill Lane, Stevenage SG1 4AB

59. East and North Hertfordshire NHS Trust, Queen Elizabeth II Hospital, Howlands, Welwyn Garden City AL7 4HQ

60. East Cheshire NHS Trust, Macclesfield District General Hospital, Victoria Road, Macclesfield SK10 3BL

61. East Kent Hospitals University NHS Foundation Trust, Buckland Hospital, Coombe Valley Road, Dover CT17 0HD

62. East Kent Hospitals University NHS Foundation Trust, Kent and Canterbury Hospital, Ethelbert Road, Canterbury CT1 3NG

63. East Kent Hospitals University NHS Foundation Trust, Queen Elizabeth The Queen Mother Hospital, St Peters Road, Margate CT9 4AN

64. East Kent Hospitals University NHS Foundation Trust, William Harvey Hospital Ashford, Kennington Road, Willesborough, Ashford TN24 0LZ

65. East Lancashire Hospitals NHS Trust, Burnley General Hospital, Casterton Avenue, Burnley BB10 2PQ

66. East Lancashire Hospitals NHS Trust, Royal Blackburn Hospital, Haslingden Road, Blackburn BB2 3HH

67. East Sussex Healthcare NHS Trust, Conquest Hospital, The Ridge, St Leonards-on-Sea TN37 7RD

68. East Sussex Healthcare NHS Trust, Eastbourne District General Hospital, Kings Drive, Eastbourne BN21 2UD

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, Wexham, 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

74. George Eliot Hospital NHS Trust, George Eliot Hospital, Eliot Way, Nuneaton CV10 7DJ

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

77. Guy's and St Thomas' NHS Foundation Trust, Guy's Hospital, Great Maze Pond, London SE1 9RT

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

80. Hampshire Hospitals NHS Foundation Trust, Basingstoke and North Hampshire Hospital, Aldermaston Road, Basingstoke RG24 9NA

81. Harrogate and District NHS Foundation Trust, Harrogate District Hospital, Lancaster Park Road, Harrogate HG2 7SX

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

84. Heart of England NHS Foundation Trust, Solihull Hospital, Lode Lane, Solihull B91 2JL

85. Hillingdon Hospitals NHS Foundation Trust, Hillingdon Hospital, Pield Heath Road, Uxbridge UB8 3NN

86. Hinchingbrooke Health Care NHS Trust, Hinchingbrooke Hospital, Hinchingbrooke Park, Huntingdon PE29 6NT

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

90. Hywel Dda University Health Board, Withybush General Hospital, Fishguard Road, Haverfordwest SA61 2PZ

91. Hywel Dda University Health Board, Prince Philip Hospital, Bryngwyn Mawr, Dafen, Llanelli SA14 8QF

92. Hywel Dda University Health Board, Glangwili General Hospital, Dolgwili Road, Carmarthen SA31 2AF

93. Hywel Dda University Health Board, Bronglais 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. King's College Hospital NHS Foundation Trust, King's College Hospital, Denmark Hill, London SE5 9RS

102. King's College Hospital NHS Foundation Trust, Beckenham Beacon, 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

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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 Alexandra 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 8RG

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. Norfok 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 Center, 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, Frognal 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

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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, Hamstel Road, Harlow CM20 1QX

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

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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

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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

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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 8XQ

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

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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

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209. St George's University Hospitals NHS Foundation Trust, St George's Hospital, Blackshaw Road, Tooting, London SW17 0QT

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212. Stockport NHS Foundation Trust, Stepping Hill Hospital, Poplar Grove, Hazel Grove, Stockport SK2 7JE

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216. United Lincolnshire Hospitals NHS Trust, Grantham and District Hospital, 101 Manthorpe Road, Grantham NG31 8DG

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## Abstract

The biochemical response to ursodeoxycholic acid (UDCA)—so-called "treatment response"—strongly predicts long-term outcome in primary biliary cholangitis (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. We performed Cox's proportional hazards regression analysis of diverse explanatory variables in a derivation cohort of 1,916 UDCA-treated participants. We used nonautomatic backward selection to derive the best-fitting Cox model, from which we derived a multivariable fractional polynomial 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. 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 (areas under the curve: >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. (HEPATOLOGY 2016;63:930-950)

Primary biliary cholangitis (PBC) is a chronic liver disease in which autoimmune destruction of the intrahepatic bile ducts results in cholestasis and progressive fibrosis.[1] 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 (APRI) 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 analyzed 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.

## Materials and 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 January 1, 2008 and July 31, 2014 or (2) liver transplant (LT) recipients who had undergone LT for PBC at any point before July 31, 2014.

Participants were recruited throughout the UK by 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 center in Northern Ireland. In collaborating centers, 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 ascertain events occurring before the date of recruitment. Participants who had not suffered an event preceding the date of recruitment were prospectively followed up until July 31, 2014.

The study was conducted in accord 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 centers. 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 centers 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 center. Follow-up CRFs were sent to the participant's current treatment center, which might also be different to the recruiting center. This was possible because all centers 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 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 hemorrhage, or hepatocellular carcinoma (HCC); (2) LT for PBC; or (3) for participants who were still alive and had never undergone LT, serum bilirubin measuring 100 $\mu$mol/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 score >49 (personal communication, NHS Blood and Transplantation; Supporting Fig. 1).[12] Furthermore, we selected the threshold, bilirubin 100 $\mu$mol/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, that is, serum sodium, creatinine, bilirubin (BIL), alanine transaminase (ALT), AST, alkaline phosphatase (ALP), platelet count, prothrombin time (PT) and international normalized ratio (INR), immunoglobulin (Ig)G, IgA, IgM, antinuclear antibodies (ANA), AMA, and anti-smooth-muscle antibodies (SMA) (presence/absence)

- Spleen size and the presence of ascites by ultra-sound scan at the time of diagnosis

- Treatment with UDCA (yes or no)

- Liver biochemistry after 12 months of treatment with UDCA (i.e., bilirubin after 12 months of UDCA [BIL12], ALT after 12 months of UDCA [ALT12], AST after 12 months of UDCA [AST12], and alkaline phosphatase after 12 months of UDCA [ALP12])

To account for interoperator 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, creatinine, BIL, ALT, AST, ALP, and immunoglobulins were treated as multiples of their respective upper reference levels. 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. Therefore, we 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 PT, 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 (interquartile range [IQR]: 9-14). 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 centers 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 (Supporting Fig. 2). 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× upper limit of normal (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's proportional hazards regression. Variables that were statistically significant at $P = 0.05$ in univariate analysis were included in a multivariable Cox model. Nonautomatic 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 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

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 preceding 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 transaminases after 12 months of UDCA (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 software (version 13.0; StataCorp LP, College Station, TX).

## Results

### Cohort Characteristics

A total of 4,099 patients with PBC were recruited to the cohort up to July 31, 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 3,165 UDCA-treated participants, whom we included in the analysis.

In these UDCA-treated participants, the year of diagnosis of PBC ranged from 1974 to 2014 (Supporting Fig. 3A). The year of diagnosis in those who had undergone LT also ranged from 1974 to 2014 (Supporting Fig. 3B). The median duration of follow-up was 6.3 years (IQR, 3.2-10.7) 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 Supporting Table 1.

### 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 modeling. After 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-baseline survival function^exp(.0287854*(alp12-xuln-1.722136304)-.0422873*(((altast12xuln/10)^-1)–8.675729006)11.4199*(ln(bil12xuln/10)12.709607778)–1.960303*(albxlln-1.17673001)-.4161954*(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% confidence interval [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 (Fig. 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 (Fig. 3). The predicted versus observed risk of an event across each decile of the 5-, 10-, and 15-year risk scores in shown in Fig. 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); 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 (Fig. 5).

## Discussion

We analyzed 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, that is, the baseline platelet count and serum albumin, and the serum bilirubin, transaminases, and ALP measured after 12 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, individualized estimates of the risk of developing ESLD within defined time points in the future. This contrasts with existing long-term prognostic models that dichotomize patients into treatment responders or nonresponders, at low or high risk of developing ESLD at an unknown point in the future (Supporting Fig. 4). 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 reevaluation 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 Supporting Document. Furthermore, Supporting 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 (1) how many risk groups should be created and (2) where (and why) to position the cutpoints. Developing sensible guidance for choosing risk groups remains a topic for further research.[21] Furthermore, we emphasise that risk must be contextualized. 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 centers 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 suboptimal 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 data set, HCC and variceal hemorrhage have not been ascertained, except as a cause of death or indication for LT. Therefore, it is uncertain whether the scoring system accurately predicts HCC or variceal hemorrhage, *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 antifibrotic 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 prerequisite 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgment

## Abbreviations

| | |
|---|---|
| **AIH** | autoimmune hepatitis |
| **ALP** | alkaline phosphatase |
| **ALP12** | alkaline phosphatase after 12 months of UDCA |
| **AMA** | anti-mitochondrial-antibody |
| **ANA** | anti-nuclear antibodies |
| **ALT** | alanine aminotransferase |
| **ALT12** | ALT after 12 months of UDCA |
| **AST** | aspartate transaminase |
| **AST12** | AST after 12 months of UDCA |
| **AUC** | area under receiver operating characteristic curve |
| **BIL** | bilirubin |
| **BIL12** | bilirubin after 12 months of UDCA |
| **CI** | confidence interval |
| **CRFs** | case record forms |

| | |
|---|---|
| **EASL** | European Association for the Study of Liver |
| **ESLD** | end-stage liver disease |
| **HCC** | hepatocellular carcinoma |
| **IgG** | immunoglobulin G |
| **INR** | international normalized ratio |
| **IQR** | interquartile range |
| **LT** | liver transplantation |
| **NHS** | National Health Service |
| **PBC** | primary biliary cholangitis |
| **PT** | prothrombin time |
| **QC** | quality control |
| **SMA** | anti-smooth-muscle antibodies |
| **TA** | transaminases |
| **TA12** | transaminases after 12 months of UDCA |
| **UCDA** | ursodeoxycholic acid |
| **ULN** | upper limit of normal |

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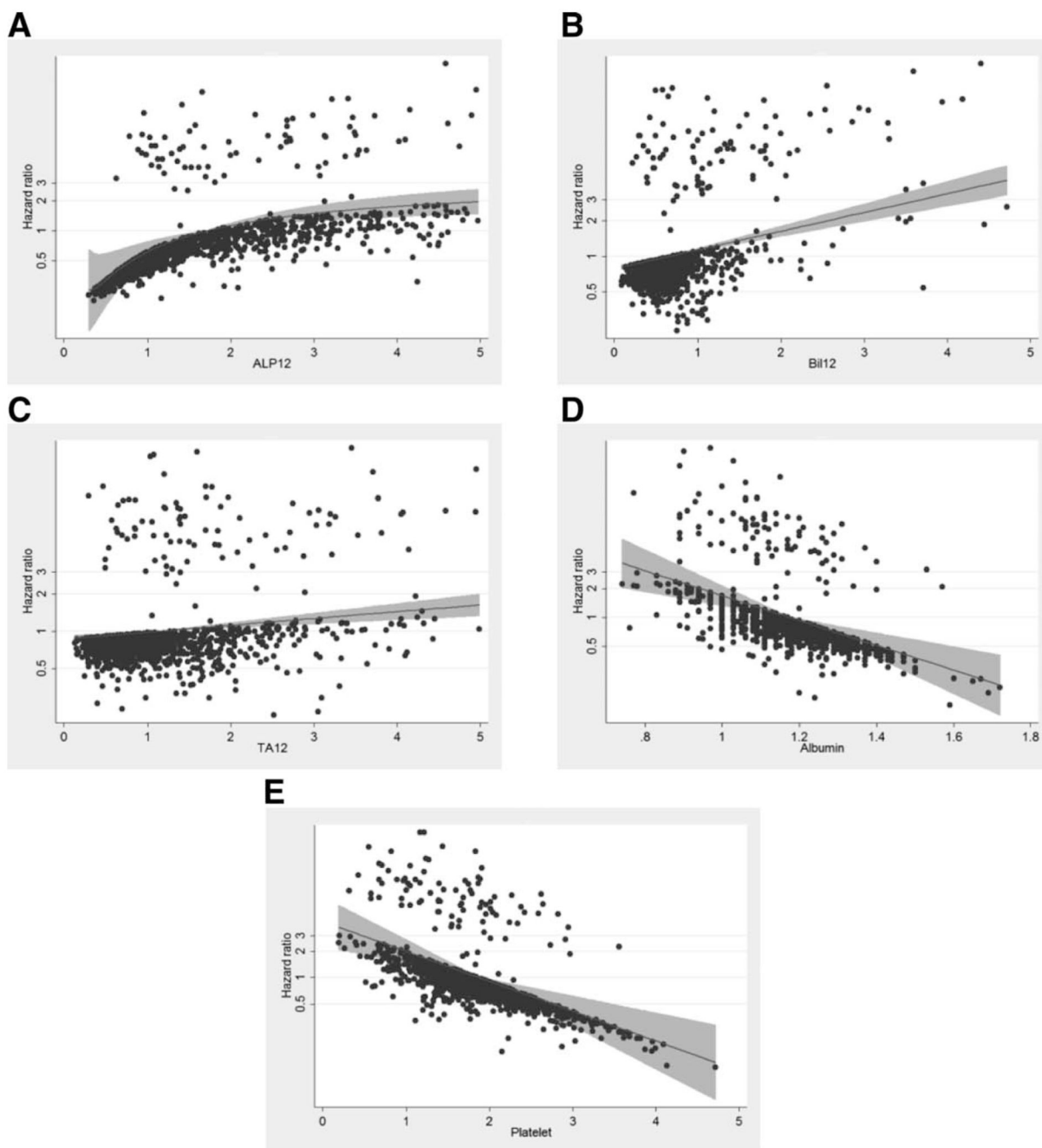
**Fig. 1.**
Relationship between the hazard ratio for a liver event (liver death or liver transplantation) and each variable within the final model together with the best-fitting polynomial line in the UK-PBC Research Cohort (A. ALP12; B. BIL12; C. TAl2; D. Albumin; E. Platelets). To allow for inter-operator variability, BIL12, TAl2 and ALP12 were analysed as multiples of their upper reference levels whereas Albumin and Platelets were analysed as multiples of their lower reference levels. The best-fitting polynomial line to describe the relationship between risk and each variable is shown. Note in particular that for each variable, risk

increases or decreases as a continuum and there are no points at which the trajectory of risk suddenly changes, which suggests they are best modelled 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 (see text). *Abbreviations*: ALP12, alkaline phosphatase after 12 months of UDCA; BIL12, bilirubin after 12 months of UDCA; LLN, lower limit of normal; ULN, upper limit of normal; TA12, transaminases after 12 months of UDCA; UDCA, ursodeoxycholic acid.
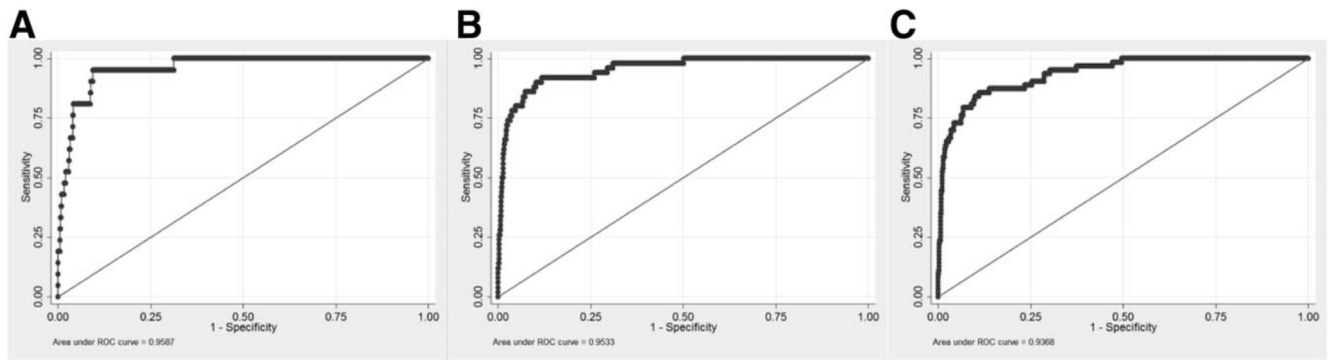
**Fig. 2.**
Receiver operating characteristic (ROC) curves for the prediction of death or liver transplantation (LT) according to the UK-PBC risk scores at 5 (A), 10 (B) and 15 years (C). *Note*: Area under the ROC curve (AUROC) can be interpreted as a summary index of classification performance. An AUC value of 0.5 indicates a 'random call,' whereas an AUC value of 1.0 indicates perfect separation of events and non events.
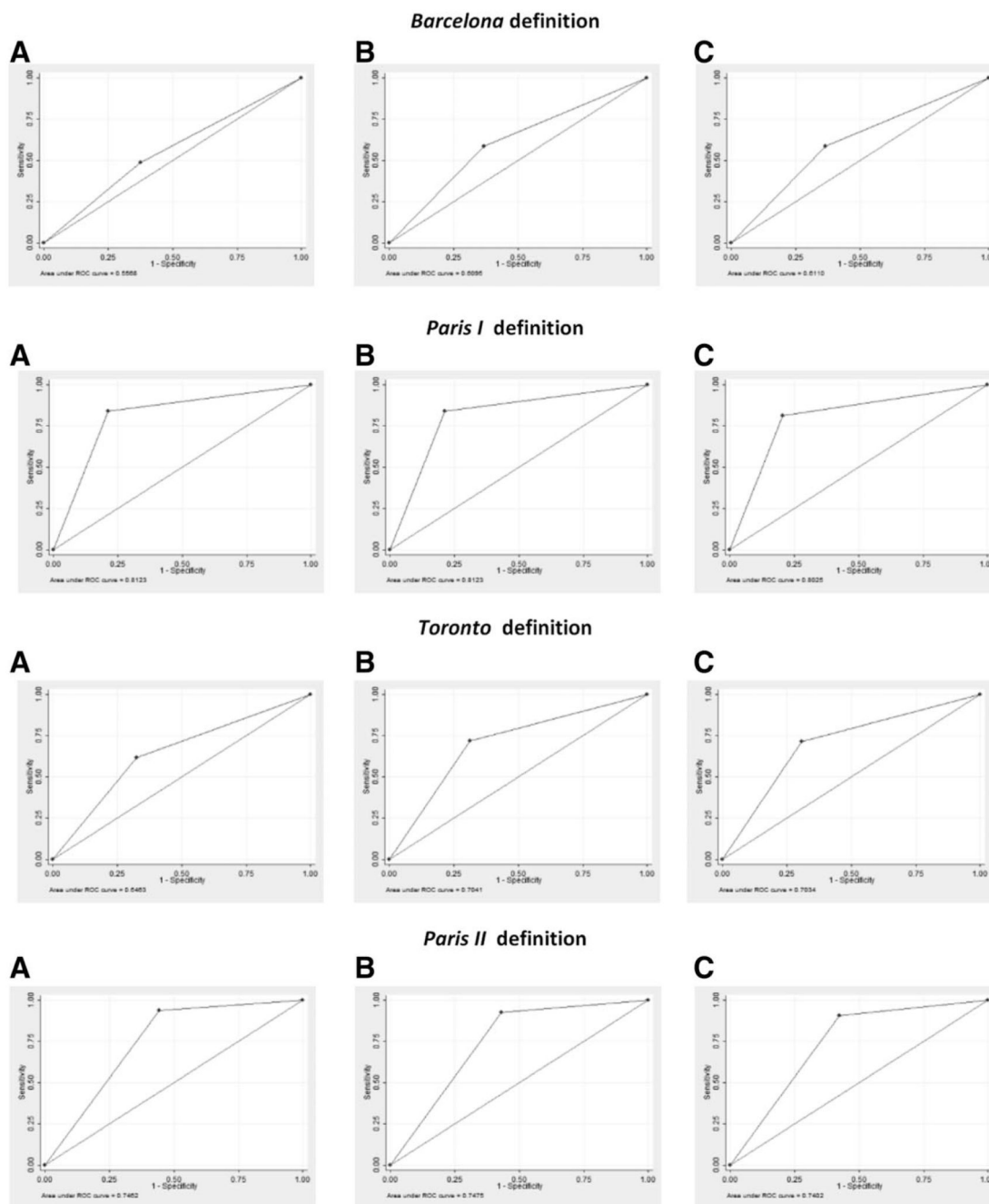
**Fig. 3.**

Receiver operating characteristic (ROC) curves for the prediction of death or liver transplantation (LT) using the *Barcelona, Paris 1, Toronto* and *Paris II* definitions of treatment response, in the UK-PBC cohort at 5 (A), 10 (B) and 15 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 pre-defined threshold and only two levels: responder and non responder. The ROC curve is therefore plotted using the single, pre defined threshold. In contrast, the UK-PBC Risk Scores are continuous. The ROC

curve is therefore plotted by incrementally varying the threshold and measuring the sensitivity and specificity at each threshold. Comparison to the Rotterdam criteria was not possible because serum albumin after 12 months of treatment was not available for all participants in the cohort.
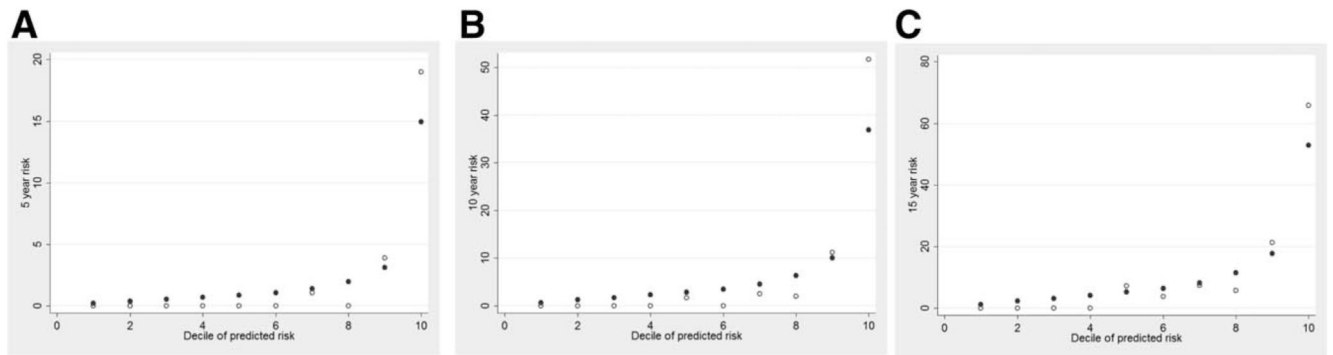
**Fig. 4.**
Predicted versus observed risk of an event across each decile of the 5 (A), 10 (B) and 15 year (C) UK-PBC risk scores. There is close correspondence between the predicted and observed risks, suggesting that the risk scores are well calibrated.
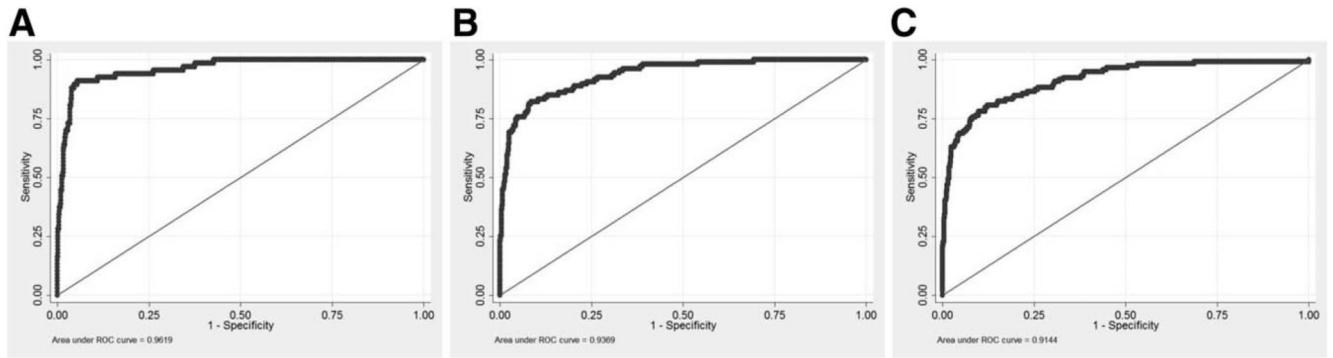
**Fig. 5.**
Receiver operator characteristic curves for the 5 (A), 10 (B) and 15 years (C) UK-PBC risk scores in the subgroup of untreated participants (n = 754)* of the UK-PBC cohort* This subgroup includes only participants who were not treated with UDCA and had been followed up for at least 12 months.

**Table 1**

**Characteristics of Patients at Baseline in the Derivation and Validation Cohorts**

| Variables[*],[†] | Derivation Cohort (N 5 1,916) | Validation Cohort (N 5 1,249) | Untreated Cohort (N 5 754)[‡] |
|---|---|---|---|
| Age, years | 55.5 (48.5-62.7) | 55.2 (47.9-62.8) | 54.0 (46.0-62.1) |
| Female, n (%) | 1,707 (89.1) | 1,140 (91.3) | 680 (90.2) |
| LT, n (%) | 155 (8.1) | 105 (8.4) | 210 (27.8) |
| ANA+, n (%) | 392 (20.5) | 250 (20.1) | 202 (26.8) |
| AMA+, n (%) | 1,667 (87.0) | 1,070 (85.7) | 679 (90) |
| SMA+, n (%) | 111 (5.8) | 91 (7.3) | 57 (7.5) |
| Splenomegaly (>12 cm), n (%) | 198 (10.3) | 97 (7.8) | 114 (15.1) |
| Ascites, n (%) | 22 (1.1) | 13 (1.0) | 20 (2.7) |
| Na ratio | 1.0 (1.0-1.1) | 1.0 (1.0-1.0) | 1.0 (1.0-1.1) |
| Creatinine ratio | 0.7 (0.6-0.8) | 0.7 (0.6-0.8) | 0.7 (0.6-0.8) |
| BIL ratio | 0.5 (0.4-0.8) | 0.5 (0.4-0.8) | 0.5 (0.4-0.9) |
| Albumin ratio | 1.2 (1.1-1.3) | 1.2 (1.1-1.3) | 1.2 (1.1-1.3) |
| ALP ratio | 1.9 (1.2-3.5) | 2.1 (1.3-3.6) | 1.5 (0.9-2.9) |
| TA ratio | 1.4 (0.9-2.3) | 1.4 (0.9-2.4) | 1.2 (0.7-2.1) |
| Platelets ratio | 1.8 (1.5-2.2) | 1.8 (1.5-2.2) | 1.8 (1.4-2.2) |
| INR | 1.0 (0.9-1.0) | 1.0 (0.9-1.0) | 1.0 (0.9-1.1) |
| IgG ratio | 0.9 (0.7-1.1) | 0.9 (0.7-1.1) | 0.9 (0.7-1.1) |
| BIL12 ratio | 0.5 (0.4-0.7) | 0.5 (0.4-0.7) | — |
| ALP12 ratio | 1.2 (0.9-2.1) | 1.3 (0.9-2.1) | — |
| TA12 ratio | 0.8 (0.6-1.3) | 0.8 (0.6-1.3) | — |
| Event rate (%) | 177 (9.2) | 114 (9.1) | 201 (26.7) |

[*] To allow for interoperator variability, the bilirubin, transaminases, alkaline phosphatase at baseline and after 12 months of UDCA, creatinine, INR, and IgG were analyzed as multiples of the upper reference level in the laboratories that measured them. The Na, albumin, and platelet count were analyzed 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**

| | Univariate Analyses | | | Multivariate Analyses | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P Value | HR | 95% CI | P Value |
| Albumin ratio | 0.007 | 0.002-0.020 | <0.001 | 0.052 | 0.013-0.211 | <0.001 |
| Platelet ratio | 0.336 | 0.247-0.457 | <0.001 | 0.362 | 0.255-0.514 | <0.001 |
| BIL12 ratio | 1.476 | 1.394-1.563 | <0.001 | 1.427 | 1.317-1.210 | <0.001 |
| TA12 ratio | 1.225 | 1.180-1.271 | <0.001 | 1.150 | 1.093-1.210 | <0.001 |
| ALP12 ratio | 1.275 | 1.216-1.337 | <0.001 | 1.103 | 1.030-1.183 | 0.005 |
| Na ratio | 0.001 | 0.001-0.002 | <0.001 | — | — | — |
| Creatinine ratio | 0.385 | 0.131-1.129 | 0.082 | — | — | — |
| BIL ratio | 1.178 | 1.148-1.208 | <0.001 | — | — | — |
| ALP ratio | 1.044 | 1.027-1.061 | <0.001 | — | — | — |
| TA ratio | 1.019 | 0.999-1.039 | 0.050 | — | — | — |
| INR | 1.420 | 0.839-2.401 | 0.191 | — | — | — |
| IgG ratio | 2.430 | 1.676-3.523 | <0.001 | — | — | — |
| Age, years | 0.970 | 0.955-0.984 | <0.001 | — | — | — |
| Year of diagnosis | 0.941 | 0.919-0.964 | <0.001 | — | — | — |
| Female | 0.816 | 0.443-1.503 | 0.514 | — | — | — |
| ANA+ | 1.423 | 0.937-2.1 | 0.048 | — | — | — |
| AMA+ | 1.090 | 0.589-2.020 | 0.782 | — | — | — |
| SMA+ | 1.114 | 0.563-2.020 | 0.756 | — | — | — |
| Splenomegaly | 8.453 | 5.969-11.971 | <0.001 | — | — | — |
| Ascites | 11.732 | 6.283-21.905 | <0.001 | — | — | — |

Splenomegaly refers to a spleen length >12 cm.

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; CI, confidence interval; HR, hazard ratio; IgG, immunoglobulin G; INR, international normalized ratio; n, number; SMA, anti-smooth muscle antibodies; TA12, transaminases after 12 months of UDCA.