Original article

Prediction of <u>s</u>urvival <u>a</u>fter <u>l</u>ung <u>t</u>ransplantation at <u>o</u>ne year (SALTO cohort) using information available at different key time-points

Yaniss Belaroussi[1,2] MD, MSc, Romain Hustache-Castaing[1] MD, Jean-Michel Maury[3] MD PhD, Laurent Lehot[4] Meng, MSc, Arnaud Rodriguez[1] MD, Xavier Demant[5] MD, Hadrien Rozé[6] MD PhD, Geoffrey Brioude[7] MD, Xavier-Benoit D'Journo[7] MD PhD, Gabrielle Drevet[3] MD, Francois Tronc[3] MD PhD, Simone Mathoulin-Pélissier[2,8] MD PhD, Jacques Jougon[1] MD PhD, Pascal-Alexandre Thomas[7] MD PhD, Matthieu Thumerel[1,9] MD PhD

1. Department of Thoracic Surgery, Haut-Leveque Hospital, Bordeaux University, Bordeaux, France.
2. Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, Epicene team, UMR 1219, F-33000, Bordeaux, France.
3. Department of Thoracic Surgery and Lung Transplantation, Hôpital Louis Pradel, Hospices Civils de Lyon, Lyon, France
4. Public Health engineer, independent epidemiologist and bio-statistician
5. Department of Pneumology, Haut-Leveque Hospital, Bordeaux University, Bordeaux, France
6. Department of Anesthesiology and Critical Care, Haut-Leveque Hospital, Bordeaux University Hospital, Pessac, 33600, France
7. Department of thoracic surgery and oesophageal diseases, Hopital-Nord-APHM, Aix-Marseille University, 13915 Marseille, France.
8. Clinical and Epidemiological Research Unit, INSERM CIC1401, Institut Bergonié, F-33000, Bordeaux, France.
9. Inserm, Centre de Recherche Cardio-thoracique de Bordeaux, U 1045 & CIC 1401, Pessac, France.

CORRESPONDING AUTHOR:

Dr. Yaniss Belaroussi, MD

Department of Thoracic Surgery, Haut-Leveque Hospital, Bordeaux University, 33604, Pessac, France.

Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, Epicene team, UMR 1219, F-33000, Bordeaux, France.

Phone: +33 6 28 96 23 28

Fax: +33 5 57 65 60 21

yaniss.belaroussi@chu-bordeaux.fr / yanissbelaroussi@gmail.com

DATA AVAILIABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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VISUAL ABSTRACT

Key question: What is the survival after lung transplantation at one-year at major stage of the lung transplantation process?

Key findings: Individual probability of survival one year after lung transplantation can be estimated at three different time-points.

Take home message: The models are clinically relevant as they provide individualized predictions of mortality according to each patient's unique situation.

4

1   **Background:** Lung transplantation is the final treatment option for end-stage lung disease. In

2   this study, we evaluated the individual risk of 1-year mortality at each stage of the lung

3   transplantation process.

4   **Methods:** This was a retrospective analysis of patients undergoing bilateral lung

5   transplantation between January 2014 and December 2019 in three French academic centers.

6   Patients were randomly divided into development and validation cohorts. Three multivariable

7   logistic regression models of 1-year mortality were applied (A) at recipient registration, (B) the

8   graft allocation, and (C) after surgery. The 1-year mortality was predicted for individual patients

9   assigned to three risk groups at time points A–C.

10 **Results:** The study population consisted of 478 patients with a mean (SD) age of 49.0 (14.3)

11 years. The 1-year mortality rate was 23.0%. There were no significant differences in patient

12 characteristics between the development (n = 319) and validation (n = 159) cohorts. The

13 models analyzed recipient, donor, and intraoperative variables. The discriminatory power (area

14 under the receiver operating characteristic curve) was 0.67 (0.62 - 0.73), 0.70 (0.63 - 0.77),

15 and 0.82 (0.77 - 0.88), respectively, in the development cohort, 0.74 (0.64-0.85), 0.76 (0.66 -

16 0.86) and 0.87 (0.79 - 0.95), respectively, in the validation cohort. Survival rates were

17 significantly different among the low- (< 15%), intermediate- (15%–45%), and high-risk (>

18 45%) groups in both cohorts.

19 **Conclusions:** Risk prediction models allow estimation of the 1-year mortality risk of individual

20 patients during the lung transplantation process. These models may help caregivers identify

21 high-risk patients at times A–C, and reduce the risk at subsequent time-points.

5

22 **ABBREVIATIONS**

23 AUC: areas under the receiver operator characteristic curves

24 CMV: cytomegalovirus

25 COPD: chronic obstructive pulmonary disease

26 ECMO: extracorporeal membrane oxygenation

27 ICU: intensive care unit

28 SALTO: survival after lung transplantation at one-year

29 SD: standard deviation

6

INTRODUCTION

Bilateral lung transplantation is the final therapeutic option in the end stage of lung diseases [1]. Survival after lung transplantation has improved due to improvements in donor selection, organ preservation, and the management of patients in the early postoperative period, and the 1-year survival rate has increased from 70% in 1988–1992 [2] to 85% according to the 2019 International Society for Heart and Lung Transplantation Registry [3].

The median survival of bilateral lung transplantation recipients is 8.8 years (conditional on survival to 1 year after transplant) [4], and predicting 1-year survival is challenging [5]. Some predictive scores have been developed to estimate 1-year survival after double lung transplantation. However, these previous studies considered only donor characteristics [6], recipient- and donor-specific characteristics [7], or postoperative events [8].

None of the models described in the literature integrated all stages of the lung transplantation process.

Bilateral lung transplantation involves a number of steps, including recipient registration on a waiting list [9,10], donor lung selection [11], treatment allocation [12], and the surgical procedure itself [13].

This study was performed to predict survival after lung transplantation at one-year (SALTO) at three time points: (A) recipient registration on the waiting list; (B) graft allocation; and (C) after the surgical procedure. Three risk groups were distinguished at each time point to help physicians reduce the risk at subsequent time points.

MATERIAL AND METHODS

Ethics Statement

The study received Institutional Review Board (Société Française de Chirurgie Thoracique et Cardio-Vasculaire) approval (IRB00012919). Patients provided informed consent for data collection before the lung transplantation procedure. This study was approved for retrospective data collection (CNIL MR-004 2223379-08/25/2021).

Settings and study population

The study population consisted of patients aged ≥ 15 years who underwent lung transplantation between January 2014 and December 2019 at one of three French academic centers. Patients undergoing single lung transplantation, or simultaneous solid organ transplantation were excluded, as were those with previous lung transplantation.

Patient data were encrypted and pseudonymized to comply with international data privacy requirements. The study was designed in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

Primary outcome

The primary endpoint was 1-year mortality, defined as death from any cause within 365 days after lung transplantation surgery.

Variables

Recipient, donor, and intraoperative variables were collected from the national database of the Agence de la Biomédecine, and from medical reports. Operative reports were screened for important intraoperative variables (intraoperative events, pleural adherence, and difficulty in performing anastomosis). An intraoperative event was defined as one of the following: major bleeding (> 1,000 mL or a major hemorrhagic event during the operation), hemodynamic failure

74 (systolic blood pressure < 50 mmHg) treated with high-dose catecholamines or extracorporeal

75 assistance, cardiac arrest, or visual pulmonary edema.

Development and validation cohorts

77 The study population was randomly assigned to the development and validation cohorts (ratio

78 of 2:1) using R Software. The two cohorts were compared according to baseline recipient-,

79 donor-, and intraoperative-specific variables, to ensure the reliability of randomization. A

80 predictive model was constructed based on the development cohort data set and then applied

81 to the validation cohort.

Statistical analysis

83 Categorical variables are presented as number (percentage) and continuous variables as the

84 mean (standard deviation, SD). Continuous variables were compared with Student's t test.

85 Categorical variables were compared with the chi-squared test and Fisher's exact test

86 according to the expected number of subjects. Statistical analyses were performed using

87 RStudio (version 4.0.3; R Development Core Team, Vienna, Austria).

88 Three predictive models were constructed to estimate the 1-year probability of survival at

89 registration on the transplantation list (based on recipient variables; model A), at the time of

90 graft allocation (based on recipient and donor variables; model B), and at the end of the lung

91 transplantation procedure (based on recipient, donor, and intraoperative variables; model C).

92 A data steering committee, including two surgeons and an epidemiologist, overviewed the

93 operative reports. Sixteen reports lacked data and were excluded from the development

94 process for model C. However, these patients were included during the development of models

95 A and B.

96 A univariable logistic regression model was applied to the development cohort to identify

97 potential factors predicting 1-year mortality. Variables with a p-value < 0.25 in the exploratory

98 analysis were incorporated into a multivariable model using backward stepwise regression.

99   The model with the lowest Akaike information criterion (AIC) was considered the most

100   accurate. The above procedure was performed for each of the three models. Variables

101   retained in model A were force-entered into the multivariable regression model during the

102   construction of models B and C. A maximum ratio of one parameter for five events was used

103   in the final models [14]. The interactions between selected factors and pathology were tested.

104   Variable linearity was tested using polynomial regression. The collinearity of the variates in the

105   models were assessed using the VIF function (Variance Inflation Factor).

106   The predictive variables for each model were allocated scores corresponding to their linear (β)

107   coefficients. All patients were assigned a final score corresponding to the sum of their β-

108   coefficients in all three models. The predicted 1-year probability of mortality was calculated for

109   each patient at each time point (A–C), and associated with the final score according to a

110   mathematical formula. Therefore, each patient had three probabilities of mortality, expressed

111   as percentages.

112   The models were then applied to the validation cohort. The areas under the receiver operator

113   characteristic curves (AUCs) were used to determine the discriminatory power of the predictive

114   models. We performed bootstrap calculation of the AUC within 1000 re-samplings for validation

115   [15] We investigated the calibration and the overall performance of the models by analyzing

116   Brier's score, calibration slope and calibration-in-the-large [16]. The data steering committee

117   defined thresholds for dividing the patients into three groups according to the predicted

118   probability of mortality: low risk (< 15%), intermediate risk (15–45%), and high risk (> 45%).

119   The predictive accuracy of each model was determined by comparison of the observed and

120   predicted events. Survival analysis was performed using Kaplan-Meier method. We performed

121   decision curve analyses using 'dcurves' package.

122   In all analyses, $p < 0.05$ was taken to indicate statistical significance.

RESULTS

The study population consisted of 478 patients (Figure 1). The mean (SD) age of the recipients was 49.0 (14.3) years and 42.9% were women. Chronic obstructive pulmonary disease (COPD, 36.8%) and cystic fibrosis (25.3%) were the most common diagnoses. More than 10% of the population (12.6%) had at least one previous thoracic surgery, 5.9% had a history of cancer, 17.6% had diabetes mellitus, 4.2% had a psychiatric disease, and 4.2% had a history of venous thromboembolism. A total of 75 patients were managed in the intensive care unit (ICU) and 25 (5.2%) required extracorporeal membrane oxygenation (ECMO) before lung transplantation.

The mean (SD) age of the donors was 47.7 (15.7) years and 46.0% were women. The main cause of death was vascular events (56.3%) and the mean (SD) duration of mechanical ventilation before organ retrieval was 2.47 (2.0) days. Among the donors, 37.7% were smokers and 5.5% had a history of pulmonary disease.

Cytomegalovirus (CMV) mismatch (donor-positive [D^+] and recipient-negative [R^-]) occurred in 13.4% of cases and sex-matched lung transplantation was performed in 67.2% of cases.

The mean (SD) operative duration was 373.0 (86.6) minutes and the mean (SD) ischemic time for the second implanted lung was 381.7 (66.2) minutes. Intraoperative assistance was used in 70.7% of procedures, consisting of cardiopulmonary bypass and ECMO in 54.8% and 45.2% of cases, respectively. Intraoperative assistance was used in 80% of the cases in the early period (2014-2015) versus 45% in the late period (2018-2019). The mean (SD) arterial oxygen partial pressure to fractional inspired oxygen ratio (PaO_2/FiO_2 ratio) at the end of the procedure was 247.8 (115.40) mmHg. A total of 108 patients died within 1 year after lung transplantation (Figure 2).

The main recipient, donor, and intraoperative variables were comparable between the development and validation groups (Table S1). Mean (SD) follow-up time was 35 months (25).

148 The 1-year mortality rate was higher in the development than validation cohort, although the

149 difference was not significant (25.1% vs. 17.6%, *p* = 0.0848).

Univariable regression analysis

151 The data steering committee selected variables considered as relevant for analysis. Finally,

152 147 variables were included in the univariable regression analysis (Supplementary Material

153 Table S2).

154 Recipient variables at registration, donor variables, intraoperative variables, and variables

155 reflecting recipient status at the end of the procedure (impossibility of weaning off assistance,

156 PaO_2/FiO_2 ratio at the end of the procedure, norepinephrine) were tested in multivariable

157 models (Supplementary Material Table S3). Three multivariable models were finally obtained

158 (Table 1) for each time point and applied to all patients (Supplementary Material S4). The

159 collinearity of the variates in the models were low (Variance Inflation Factor inferior to 5).

160 The distributions of scores A–C were similar between the development and validation cohorts

161 (*p* = 0.982, *p* = 0.611, and *p* = 0.690, respectively).

162 The correlations between the individual risk of mortality estimated using models A–C and

163 scores A–C are shown in Figure 3.

164 The probability of mortality was calculated using the equations shown in Supplementary

165 Material S5.

166 With regard to discriminatory power, the AUCs (95%CI) for models A–C were 0.67 (0.62 -

167 0.73), 0.70 (0.63 - 0.77), and 0.82 (0.77 - 0.88), respectively, in the development cohort, 0.74

168 (0.64-0.85), 0.76 (0.66 - 0.86) and 0.87 (0.79 - 0.95), respectively, in the validation cohort.

169 When using the bootstrap calculation for validation, mean AUCs were 0.69, 0.73 and 0.83 for

170 model A, B and C respectively. When investigating calibration in both cohorts, results were

171 interesting (Supplementary Material S6 – S9), and no interactions with diagnosis were

12

172 observed. Both models had low collinearity between the covariates (Supplementary Material

173 S10). Decision curve analyses showed a benefit in using the models when the probability of

174 death is higher than 10% approximately at timepoint A and B and when the probability of death

175 is higher than 5% at timepoint C (Supplementary Material S11-S13).

176 In both cohorts, the high-risk group had significantly more events in all models (Table 2), and

177 the proportion of patients who died within 1 year increased with the predicted probability of

178 death. The distribution of predicted probability of death at 1 year was similar between the

179 validation and development cohorts; however, those who had an unfavorable event at 1 year

180 had a significantly higher probability of death in all models (Figure 4).

181 Figure 5 presents a summary of the mortality prediction for each patient and time point (A–C),

182 and the risk group distributions. Patients could be classified as low, intermediate, or high risk

183 during all lung transplantation processes, but could change from one risk group to another

184 according to the prediction at the subsequent time point.

ACCEPTED MANUSCRIPT

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185 **DISCUSSION**

186 The SALTO study represents the first attempt to estimate the probability of death (and by

187 extension, survival) 1 year after lung transplantation at three different time-points before the

188 postoperative period. This approach was based on three scores: score A (4 predictive

189 variables), score B (8 predictive variables based on recipient- and donor-specific

190 characteristics), and score C (13 predictive variables based on recipient, donor, and procedure

191 characteristics). The three scores for each patient together comprised the absolute risk, i.e.,

192 survival probability, calculated prior to the postoperative period.

193 The outcomes of the study population were somewhat lower to those reported in the Registry

194 of the International Society for Heart and Lung Transplantation (77% in our population vs 81%)

195 [3,4].

196 Our models included variables considered as prognostic factors in other studies, such as

197 imaging abnormalities [17], donor oxygenation ratio [18], need for assistance at the end of the

198 procedure, and mean pulmonary arterial pressure [19]. Surprisingly, other variables such as ICU

199 hospitalization, ECMO, sex, CMV mismatch, and graft ischemia time were not included in the

200 models. For example, it has been reported that patients supported by ECMO before lung

201 transplantation have poorer short-term outcomes [20,21], but pre-operative ECMO or

202 intraoperative assistance were not included in predictive models in the present study. The high

203 rate of intraoperative assistance or the size of the population could explain that preoperative

204 ECMO or intraoperative assistance were not included in the predictive models. However, the

205 effect of intraoperative event could be captured by the intraoperative event variable in model

206 C. Moreover, if a variable was not included in our models, it does not mean it is not a prognostic

207 variable but other variables better fit with our predictive models. The small number of patients

208 included in the study (*n* = 479) and careful patient selection may have impacted the outcomes.

209 The study power may have limited the detection of factors that are associated with post-

210 transplant mortality, illustrated by the absence of variables previously identified as prognostic

14

211 factors such as ischemic time. Although variable selection can be discussed, the purpose of

212 this study was not to examine the prognostic factors themselves, but rather to achieve the

213 most accurate prediction of 1-year survival; stepwise backward selection was adequate for this

214 purpose [22]. We tested four randomization sequences, which all yielded the same combinations

215 of variables. The variables included in our models differed from those described in predictive

216 scores in previous studies [7,8,17]. Our selected variables could be considered as predictive

217 factors. However, our study design did not permit exploring causal inferences. We cannot

218 assert that the variables included in the model cause death. They may help to predict the

219 outcome.

220 As an example (supplementary material – survival probability calculator), a subject with COPD

221 and mean pulmonary arterial pressure of 18 mmHg would have an estimated probability of

222 death at time A of 11.4% (low risk). With donor characteristics (PaO_2/FiO_2 ratio of 280,

223 atelectasis and lung condensation on computed tomography (CT)), this probability would

224 increase to 20.3% (intermediate risk). With an intraoperative event (major hemorrhagic event)

225 requiring the transfusion of 6 units of red blood cells and 3.5 µg/kg/min norepinephrine at the

226 end of the procedure, the estimated probability would increase to 51.8%. This prediction

227 corresponds to the worst-case scenario; the reverse situation, i.e., changing from high to low

228 risk, was also possible, but less likely.

229 Of the three models tested, model C showed the best discrimination and calibration, which

230 was reasonable as predictions should be more accurate closer to the endpoint. However, this

231 could also be affected by the clinical course, as illustrated by the 251 patients showing a

232 change in risk group over the follow-up period. This approach could facilitate decision-making

233 during the entire process of lung transplantation, from recipient registration to surgery.

234 Despite these encouraging results, this study had some limitations. First, the small number of

235 subjects limited the number of parameters that could be analyzed [14]. The resulting AUC for

236 models A and B could be improved with a larger population. On the other hand, the small

15

237 sample size made it possible to collect complete data in a large proportion of cases. Second,

238 as some data were collected retrospectively, the analyses of certain variables could have

239 lacked accuracy, and some factors could not be integrated into our study, such as the

240 preoperative Karnofsky Performance Status score [7] and human leukocyte antigen (HLA)

241 mismatch [23]. Three centers participated in the study, and survival may have varied according

242 to the protocols used at those centers. In those three centers, the number of intra-operative

243 assistance is rather high (70%). In the early 2010s, in those centers, intra-operative assistance

244 was frequently used to benefit oxygenation and to reduce the occurrence of reperfusion

245 damage [24]. The number of intra-operative assistance reported in the European centers differs

246 from a center to another (for instance, Atchade et al. reported 75% of intra-operative

247 assistance [25] whereas 28% of the patients required intraoperative ECMO support in the Ius et

248 al study [26]). Finally, further prospective studies are needed for external validation before using

249 SALTO prediction models in clinical practice.

250 SALTO scores are clinically interesting as they could be used to predict changes in risk group

251 between time points A–C. For example, when managing a patient with a high risk of mortality

252 at time A, the goal is to decrease this risk at time B and/or C. Better graft allocation or a specific

253 surgical procedure could be discussed during the meetings pertaining to patient registration

254 for transplant. Ultimately, the aim is to achieve the lowest probability of death at time C.

255 Primary diagnostic indications for transplantation and donor characteristics have changed over

256 the past two decades (e.g., the median donor age increased by 10 years between 2000 and

257 2018)[3] and would change in the future since proportion of cystic fibrosis patients is decreasing

258 among lung transplantation population. SALTO models could be considered as an

259 actualization of the prediction approach and do not aim to substitute to lung allocation score.

260 We aimed to provide a new insight of the lung transplantation process. Variables that are not

261 captured by UNOS or ISHLT registries, particularly intraoperative variables, were collected in

16

262   order to update prediction abilities. In comparison with previous studies[6,7] based on UNOS

263   data in North American population, our models are more specific for the European population.

264   As medical knowledge and techniques evolve, additional models should be used to

265   corroborate our findings. The coefficients of the models (bêta) should be adjusted based on

266   the inclusion of additional consecutive patients, which could involve the application of artificial

267   intelligence systems [22]. The results of this study can be considered as primary data; additional

268   data could be used to improve the models automatically through artificial intelligence.

269   However, prospective studies are needed for external validation. Predictive models can be

270   updated as new data becomes available, which can help refine the models and improve their

271   accuracy over time. This can lead to more personalized and effective treatments for lung

272   transplant patients.

273   Lung transplantation is a complex procedure with many factors that can affect outcomes such

274   as donor and recipient characteristics and surgical procedure. Predictive models can be used

275   to identify patients who are at high risk of poor outcomes and who may require more aggressive

276   care or closer monitoring. However, it is important to note that predictive models should always

277   be used in conjunction with clinical judgement and should not be relied on as the sole basis

278   for clinical decision-making.

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282 **DISCLOSURES**

283 None.

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TABLES

Table 1. Multivariable logistic regression analysis of predictors of 1-year mortality

	Model A		Model B		Model C	
Variable	β	*p*-value	β	*p*-value	β	*p*-value

Recipient information

Diagnosis

Table 1. Multivariable logistic regression analysis of predictors of 1-year mortality

Cystic fibrosis	Ref[A]	Ref	Ref	Ref	Ref	Ref
Emphysema/COPD	0.9727	0.064	0.8013	0.127	1.6249	0.011
Pulmonary hypertension	0.6159	0.477	0.3806	0.671	0.5588	0.604
Fibrosis	1.6869	0.002	1.6815	0.002	1.8299	0.005
Other	1.0019	0.117	0.9733	0.126	1.2658	0.114
Psychiatric disease	1.4226	0.021	1.4650	0.024	1.6031	0.041
History of venous thromboembolism	1.7798	0.006	1.8994	0.005	1.8738	0.019
Mean pulmonary artery pressure (mmHg)						
Not measured	1.1070	0.102	1.1787	0.089	0.8225	0.344
< 20	Ref	Ref	Ref	Ref	Ref	Ref
20–40	0.9115	0.058	0.9861	0.046	1.1035	0.059
> 40	1.0695	0.107	1.0929	0.111	1.1193	0.150
Donor information						
PaO_2/FiO_2 ratio[B]	-	-	−0.0220	0.101	−0.0208	0.193
Atelectasis	-	-	0.4420	0.118	0.4456	0.181
Imaging						
Normal	-	-	Ref	Ref	Ref	Ref
≥ 1 abnormality[C]	-	-	0.3995	0.172	0.5794	0.084
Positive blood culture	-	-	0.9316	0.052	1.2666	0.023

Procedure

Intraoperative information:

Table 1. Multivariable logistic regression analysis of predictors of 1-year mortality

Major bilateral pleural adherence	-	-	-	-	1.1028	0.041
≥ 1 intraoperative event	-	-	-	-	0.3877	0.306
Red blood cell transfusion, units	-	-	-	-	0.1025	0.008
At the end of the procedure:						
Norepinephrine rate (µg/kg/min)	-	-	-	-	1.1028	0.003
Need of assistance	-	-	-	-	1.0159	0.022

[A] Ref: reference.

[B] PaO_2/FiO_2 divided by 10.

[C] Excluding atelectasis.

COPD, chronic obstructive pulmonary disease.

Table 2. One-year mortality by risk group

	Development Cohort			Validation Cohort		
	Number of events (*n*/total)	OR (95% CI)	*p*-value	Number of events (*n*/total)	OR (95% CI)	*p*-value
Model A						
Risk group			<0.001			0.009
Low-risk	13/92	Ref	Ref	3/52	Ref	Ref
Intermediate-risk	55/210	2.16 (1.11–4.18)	0.023	21/95	4.64 (1.31–16.38)	0.017
High-risk	12/17	14.58 (4.41–48.27)	<0.001	4/12	8.17 (1.53–43.52)	0.014
For 10% increase in predicted mortality risk		1.69 (1.37–2.08)	<0.001		1.53 (1.15–2.03)	0.004
Model B						
Risk group			<0.001			0.019
Low-risk	13/92	Ref	Ref	4/52	Ref	Ref
Intermediate-risk	33/166	1.8 (0.92–3.54)	0.086	15/72	2.91 (0.92–9.2)	0.068
High-risk	34/61	11.31 (4.43–28.85)	<0.001	9/35	6.46 (1.64–25.5)	0.008
For 10% increase in predicted mortality risk		1.72 (1.44–2.06)	<0.001		1.43 (1.11–1.84)	0.005
Model C						
Risk group			<0.001			<0.001
Low-risk	11/132	Ref	Ref	2/64	Ref	Ref
Intermediate-risk	33/129	3.78 (1.82–7.87)	<0.001	8/57	5.06 (1.03–24.92)	0.046
High-risk	31/47	21.31 (8.99–50.52)	<0.001	15/33	25.83 (5.4–123.67)	<0.001
For 10% increase in predicted mortality risk		1.74 (1.5–2.02)	<0.001		1.67 (1.36–2.05)	<0.001

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Ref: reference

FIGURES

Central Image. Estimation of the survival probability at one year after lung transplantation at three key time-points: pre-allocation (probability A), graft allocation (probability B) and after lung transplantation (probability C).

Figure 1. Flow chart of the study population.

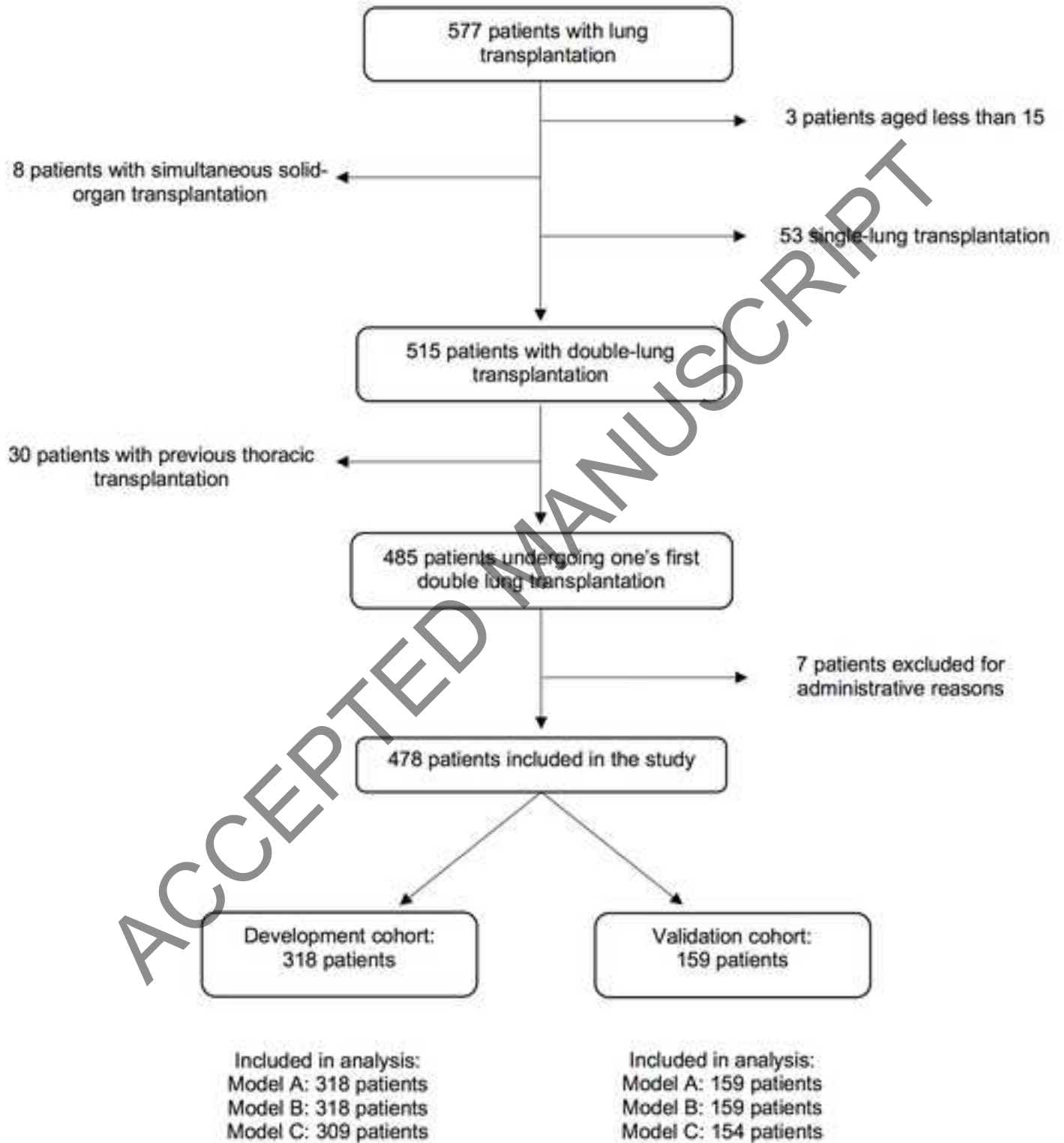Figure 2. Kaplan Meier survival curve of overall population.

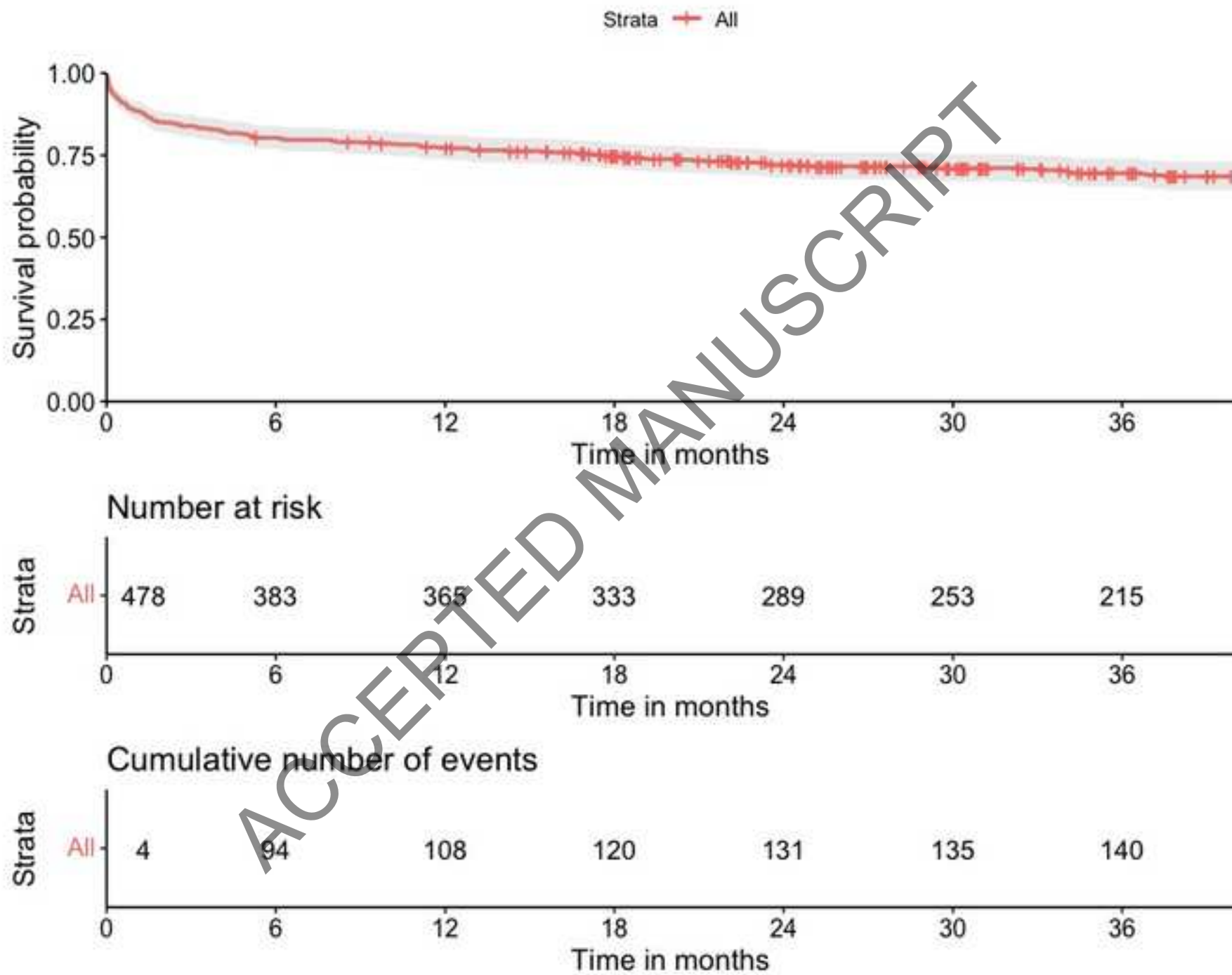Figure 3. Probability of death at 1 year according to the calculated scores.

Figure 4. Predicted probability of death in models A–C. Part 1: red, patients who died within 1 year; green, patients alive at 1 year. Part 2: red, patients who died within 1 year; green, patients alive at 1 year. * $p < 0.01$.
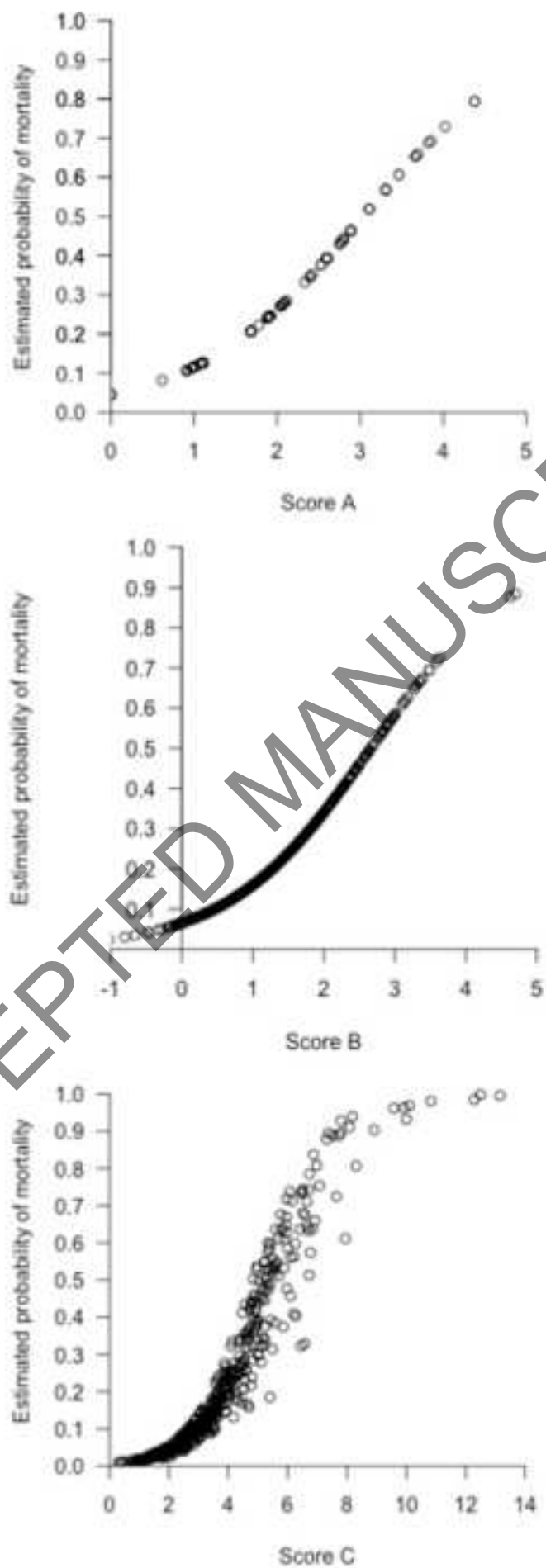
Figure 5. Risk group according to calculated model scores: 16 patients had no score for model C.

Central Image. Estimation of the survival probability at one year after lung transplantation at three key time-points : pre-allocation (probability A), graft allocation (probability B) and after lung transplantation (probability C).
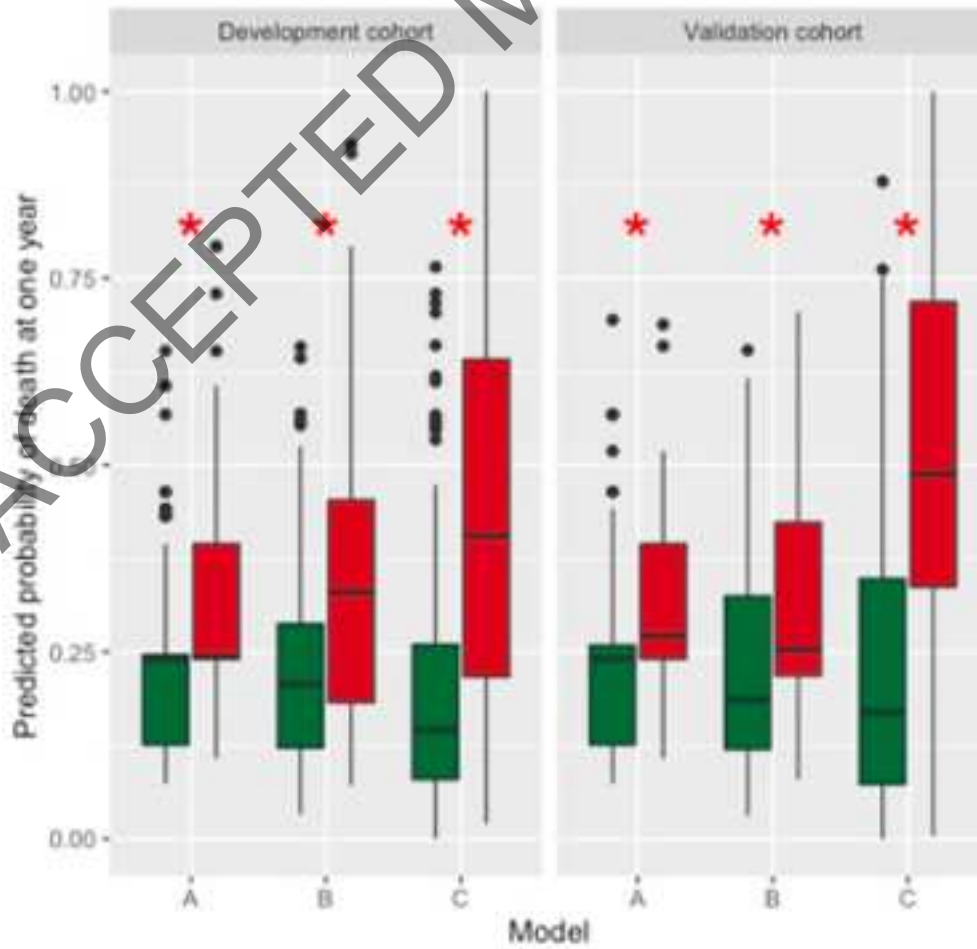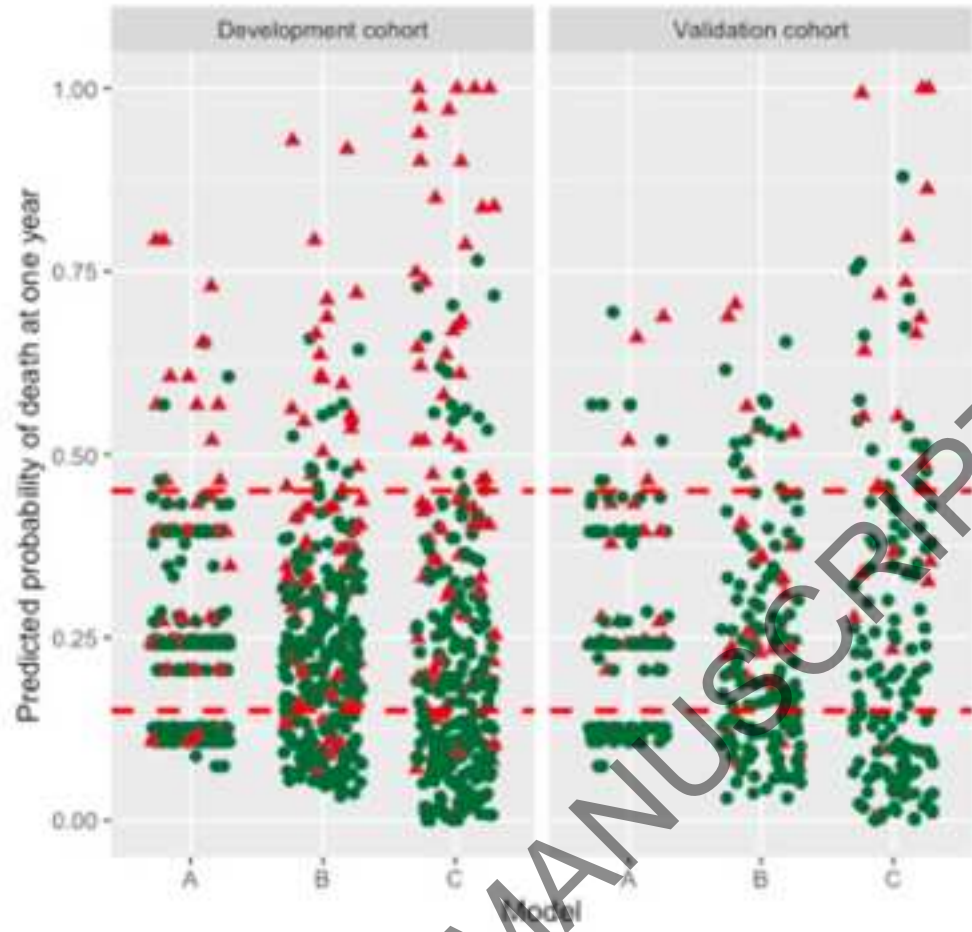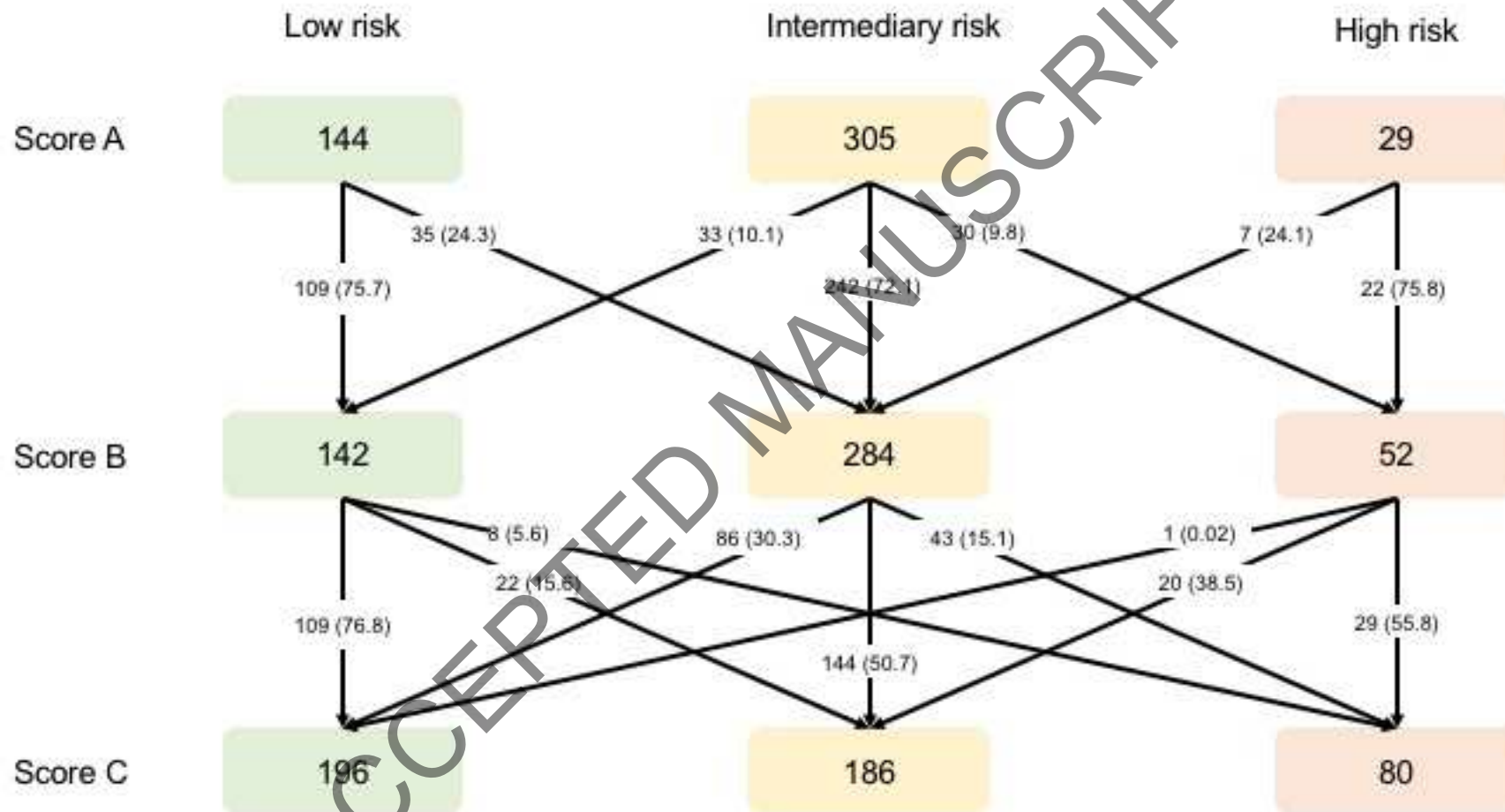
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Figure 1

577 patients with lung transplantation

3 patients aged less than 15

8 patients with simultaneous solid-organ transplantation

53 single-lung transplantation

515 patients with double-lung transplantation

30 patients with previous thoracic transplantation

485 patients undergoing one's first double lung transplantation

7 patients excluded for administrative reasons

478 patients included in the study

Development cohort: 318 patients

Validation cohort: 159 patients

Included in analysis:
Model A: 318 patients
Model B: 318 patients
Model C: 309 patients

Included in analysis:
Model A: 159 patients
Model B: 159 patients
Model C: 154 patients

Figure 2

Click here to access/download;Figure;Figure 2.jpeg ⬇

Strata ╋ All

Number at risk

Cumulative number of events

Figure 3

Figure 4

Figure 5