Utility of the IMPACT score for predicting heart transplant mortality. Analysis on a contemporary cohort of the Spanish Heart Transplant Registry

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Abstract

Introduction and objectives. The Index for Mortality Prediction After Cardiac Transplantation (IMPACT) score was derived and validated as a predictor of mortality after heart transplantation (HT). The primary objective of this work is to externally validate the IMPACT score in a contemporary Spanish cohort.

Methods. Spanish Heart Transplant Registry data were used to identify adult (>16 years) HT patients between January 2000 and December 2015. Retransplantation, multiorgan transplantation and patients in whom at least one of the variables required to calculate the IMPACT score was missing were excluded from the analysis (N = 2810).

Results. Median value of the IMPACT score was five points (IQR: 3, 8). Overall, 1-year survival rate was 79.1%. Kaplan-Meier 1-year survival rates by IMPACT score categories (0–2, 3–5, 6–9, 10–14, ≥15) were 84.4%, 81.5%, 79.3%, 77.3%, and 58.5%, respectively (Log-Rank test: p < .001). Performance analysis showed a good calibration (Hosmer-Lemeshow chi-square for 1 year was 7.56; p = .47) and poor discrimination ability (AUC-ROC .59) of the IMPACT score as a predictive model.

Conclusions. In a contemporary Spanish cohort, the IMPACT score failed to accurately predict the risk of death after HT.

Keywords. Graft survival; Heart transplantation; Organ allocation; Prognostic model research.

1 INTRODUCTION

Heart failure is one of the most important public health problems due to its associated morbimortality and high healthcare cost. Despite the advances in evidence-based medical treatment in the last decades, long-term survival of advanced heart failure (AHF) patients is dismal.[1] Heart transplant (HT) remains as the gold standard of care for some AHF patients with current 1-year survival rates of 86% and median survival of 12.5 years.[2] However, the low organ availability makes imperative a risk stratification of patients undergoing HT to improve outcomes. In this regard, several prognostic models have been developed in the last decade. Among them, the Index for Mortality Prediction After Cardiac Transplantation (IMPACT) score, a prognostic model based on recipient´s clinical variables, is the most relevant model in terms of prognostic research. This score was originally designed using data from the American United Network for Organ Sharing (UNOS) registry[3] and externally validated in a series of more than 29 000 patients from the International Society of Heart and Lung Transplantation (ISHLT) registry, demonstrating a good correlation between the observed and expected mortality.[4]

However, according to the standards in prediction model research, before implementing a risk score in daily clinical decision-making, its performance in a different cohort from which it was derived and the impact in clinical practice or prognosis should be evaluated.[5, 6] The Spanish HT system has certain characteristics that differentiate it from other countries, such as older donors age, shorter waiting-list times and a high rate resolution for urgency status patients.[7] Therefore, the aim of this study is to perform a geographical external validation study of the IMPACT score in a contemporary Spanish HT cohort, describing both the calibration and discrimination ability of this prognostic model.

2 MATERIALS AND METHODS

2.1 Study design, data source, and study population

This is a multicenter, observational, and retrospective study of patients consecutively who underwent orthotopic HT in Spain. Donors and recipients' demographic variables, as well as surgery, immunosuppression and follow-up data, were prospectively recorded in the

Spanish Heart Transplant (SHT) registry. This registry was approved by the ethical committees of the participating centers and its compliance is mandatory.

For the purpose of this study, adult (>16 years old) HT consecutively performed between January 2000 and December 2015 were included. Those patients who underwent retransplantation or combined organ transplantation were excluded from the analysis. Likewise, the lack of any of the essential variables to calculate the IMPACT score was a reason for exclusion.

2.2 Definition of the study variables

The variables included in the analysis were those derived from the original study by Weiss et al. and that led to the IMPACT score generation (Table **1**).[3] All these data, with the exception of race and dialysis, were available in the database of the SHT registry. The variables race and pre-transplant dialysis were obtained from the individual review of the medical records of each patient by the responsible center. The Cockcroft-Gault formula was used to calculate the creatinine clearance: {[140-age (years)] × weight (kg) / [72 × serum creatinine (mg/dL)]} × (.85 in women). The IMPACT score was calculated for each individual patient, with a maximum score of 50 points. Patients were stratified according to different categories of the IMPACT score: 0–2 points, 3–5 points, 6–9 points, 10–14 points, and ≥15 points.

2.3 Statistical analysis

Continuous variables with normal distribution were expressed as mean and standard deviation (SD). Non-normally distributed continuous variables were expressed as median and interquartile range. Dichotomous categorical variables were expressed as frequency along with percentages.

The primary objective was 1-year mortality after HT. Kaplan-Meier survival analysis were performed for the overall cohort and for the different IMPACT score categories. Log-rank test was used to compare the different survival curves. Calibration and discrimination were determined to assess the performance of the IMPACT score as a predictive model. Calibration was assessed by the Hosmer-Lemeshow goodness of fit test, for which patients were grouped into deciles according to the model's predicted risk.

The area under the receiver-operating curve (AU-ROC) was used to determine the discrimination ability of the IMPACT score to predict 1-year mortality.

3 RESULTS

During the study period, 4216 adult HT were performed. Of them, 1406 were excluded from the analysis due to retransplantation, combined organ transplantation and lack of at least one of the essential variables for the calculation of the IMPACT score, being 2810 adult HT our final study cohort (Figure **1**).

The overall cohort had a median IMPACT score of five points (IQR: 3, eight points) with a range of 0–27 points. Figure **2** shows the distribution of the different IMPACT score values in the study cohort. Table **2** shows the baseline characteristics of the study cohort. Mean ± SD age was 52.8 ± 11.6 years, 78.4% of the patients were male and almost all patients were Caucasian (99.6%). Median bilirubin was 1 mg/dl (IQR: .64, 1.64 mg/dl) and the median creatinine clearance was 74.02 ml/min (IQR: 56.2, 95.7 ml/min). The most common heart failure etiologies were dilated ischemic cardiomyopathy (41.5%) and idiopathic cardiomyopathy (28.3%). Regarding the clinical condition prior to HT, 1.5% required dialysis, 13.7% were under mechanical ventilation and 13.2% had previous infection. Almost three-quarters of the cohort were transplanted without the need for mechanical circulatory support (73.3%). However, 15.3% of the study cohort were transplanted under an intra-aortic balloon pump, 10% under TMCS, 1.2% under pulsatile VADs and only .2% under continuous flow VADs.

3.1 Survival analysis

Kaplan-Meier survival analysis showed an overall 1, 5, and 10-year survival rates of 79.1%, 68.9%, and 57.7%, respectively, with a median survival of 12.5 years (Figure **3A**). One-year survival was mainly conditioned to the first month after HT, where survival rate was 87.3%, while survival rates at 3 and 6 months were 83.2% and 81.3%, respectively (Figure **3B**).

On the other hand, Kaplan-Meier 1-year survival curves analysis stratified by different categories of the IMPACT score showed a significant inverse association between the IMPACT score and 1-year survival, so that the higher the IMPACT score the lower 1-

year survival. In particular, 1-year survival rates for the different IMPACT score categories (0–2, 3–5, 6–9, 10–14 and ≥ 15) were 84.4%, 81.5%, 79.3%, 77.3%, and 58.5%, respectively ($p < .001$) (Figure **4**).

3.2 Performance of the IMPACT score

Calibration and discrimination ability were evaluated as complementary variables to determine the performance of the IMPACT score as predictive model for 1-year mortality in our cohort. Discrimination ability is poor since the AU-ROC for predicting 1-year mortality in our cohort was .59 (Figure **5**). In contrast, the Hosmer-Lemeshow chi-square for 1 year was 7.56 ($p = .47$), which indicates that the predicted mortality compared with actual mortality in our cohort is consistent, that is, there is a good calibration of the model.

4 DISCUSSION

There are several prognostic models that allow predicting short and long-term outcomes after HT. The IMPACT score was originally designed using a cohort from the UNOS registry and exclusively includes variables that reflects the clinical condition of the recipient before HT.[3] In this work, we have carried out a geographical external validation study of the IMPACT score to assess its performance as short-term prognostic model in a contemporary Spanish cohort. Our findings suggest that the performance of the IMPACT score could be poor outside the cohort from it was derived and therefore hardly applicable to our daily clinical setting.

Since its initial publication in 2011, the IMPACT score has been the most relevant HT prognostic model in terms of research and several attempts have been made to externally validate it.[8] In the work by Kilic et al., using a cohort derived from the ISHLT registry that included 29 242 adult HT performed between January 2001 and July 2010, all the variables of the IMPACT score except female sex and an intra-aortic balloon pump were associated with 1-year mortality after HT in the multivariate analysis.[4] In addition, they found a significant inverse relationship between the IMPACT score categories and 1-year survival with a good positive correlation between predicted mortality by the IMPACT score and that observed in the validation cohort (correlation coefficient $r = .87$). Although through a different statistical method, our study generates similar results bringing to light

the good calibration of the IMPACT score. However, better calibration has been suggested for other prognostic models such as the International Heart Transplant Survival Algorithm (IHTSA) score.[9]

Despite these good results, calibration alone is insufficient to assess a model's prediction capability and a second property need to be assessed, discrimination. Discrimination refers to how well the model differentiates those at higher risk of having an event from those at lower risk. Nevertheless, to date, information regarding the discrimination ability of the IMPACT score has been unflattering. Several studies have shown that the discrimination ability of the IMPACT score is, at best, modest compared to that of other new prognostic models (such as Donor Risk Index -DRI-, Transplant Risk Score and ITHSA scores) with AU-ROC or C-statistic values that vary between .52 and .65 depending on the cohorts on which they were applied.[8-12] Recently, Coutance et al. performed an extensive evaluation of the statistical performance of 16 different predictive models aimed at stratifying the risk of early HT failure (death or retransplantation) based on preoperative variables in a large contemporary cohort of 9,396 HT recipients derived from the UNOS database (2014-2017).[13] They found that all risk scores were significantly associated with post-HT outcomes. However, their statistical performance was poor (C-statistic ranged from .544 to .646) and varied across subgroup of patients (older donors, older recipients and types of mechanical circulatory support). According to these data, the discrimination ability of the IMPACT score in our cohort is poor, being almost similar to that determined by chance.

Probably, the main explanation for this consistent lack of predictive strength showed by the IMPACT score in the literature is that it only takes into account recipient´s variables, ignoring those variables related to the donor, surgery or the transplant center, which have shown to be thoroughly correlated with short-term outcomes after HT.[14-18] Noteworthy, when different clinical prognostic models are analyzed, such as IMPACT, DRI and Risk Stratification Score (RSS),[19] the three methods use quite different sets of clinical characteristics.[20] In fact, there is no variable that has been used simultaneously by the three prognostic models. However, when all the variables included in these three models are taken into account, their discrimination ability has been shown to be similar to that of machine learning models, suggesting that when taken together, the three main clinical prognostic methods identify the most relevant characteristics associated with post-HT

outcomes.[20] Another determining factor for the lack of predictive precision stems from the inherent limitations of regression models. Most of the commonly used clinical approaches to predict survival use one-size-fits-all models without taking into account the heterogeneity of the donor and recipient populations, the influence of certain characteristics (covariates) and their interactions in survival, and that the weight of different characteristics on post-HT survival depends on the time elapsed since HT.[20]

Another important issue derived from our series is that, although mortality in our series is in accordance with that expected according to the IMPACT score, 1-year survival in our series is slightly lower compared with that observed in the derivation and external validation series of the IMPACT score (87% vs. 85% vs. 79%, respectively).[3, 4] There are several factors to take into account when addressing these differences. Firstly, these results may be influenced by the fact that the SHT registry is mandatory while the ISHLT registry is voluntary, which can lead to an information bias. On the other hand, as we previously mentioned, certain variables related to the donor have a negative impact on the short-term prognosis after HT. Donor age is a well-known predictor of graft loss at 1 year and its implication in HT prognosis has been largely demonstrated, increasing mortality by around 20% for every 10 years.[11, 13, 16, 19, 21] Unlike the ISHLT series, where the mean donor age remains stable around 35 years,[14] in Spain we have witnessed a progressive increase in the mean donor age, being nowadays almost 45 years.[15] Similarly, rates of gender mismatch for male recipients, which has been shown to increase 1-year mortality by 40%,[22] are significantly higher in our series compared to the data from the ISHLT registry (22% vs. 16%).[14]

However, probably the most determining factor for the worst short-term results in our series is that our patients underwent HT in a worse clinical condition. This feature is particularly important when interpreting our results, since it represents the main difference between our series and the IMPACT score´s derivation and validation cohorts. Unlike these series, the rates of mechanical ventilation and TMCS in our series are significantly higher (2.7% vs. 2.8% vs. 13.7% and 1.4% vs. 1.7% vs. 10%, respectively), being both variables the ones with the greatest prognostic weight in the original model.[3] Accordingly, a recent meta-analysis that included almost 282,400 transplant patients from 62 studies confirmed that the variables most influencing 1-year mortality after HT are mechanical ventilation and the need for TMCS, so that each of these variables increases

2.5 times 1-year mortality.[16] Among patients bridged with TMCS, with the exception of some single-center series,[23] those supported with ECMO have been consistently associated with worse prognosis compared to other devices with reported 1-year survival rates ranging from around 60%–70%.[24-27]

4.1 Study limitations

Firstly, the results of this work have limitations derived from the retrospective analysis of a registry´s database: the quality of the source data, the number of missing data, and the lack of standardization associated with multicenter studies. Second, given the 15-year study period, it is likely that there are temporal variations in surgical strategies, immunosuppression regimens, and center-specific protocols. Third, we have excluded almost 30% of patients from the initial cohort due to missing values, which may affect the results of our study. Although multiple imputation is the suggested method to replace omitted information, there is a high proportion of missing values in certain main variables, where the use of imputation could put the statistical credibility of these variables at risk. Furthermore, we have compared the patients excluded and included in the study, finding some significant differences between the two groups but probably irrelevant from a clinical point of view due to the slight magnitude of these differences (**Supplementary Table S2**). Accordingly, we decided not to perform the imputation of missing values. Finally, the results of the study may not be applicable to patients who undergo retransplantation or multiorgan transplantation as they were not included in this study due to their small sample size and the specific additional risks of these patients.

5 CONCLUSIONS

In conclusion, we have carried out an external geographic validation study of the IMPACT score in a contemporary Spanish cohort. Our results showed a good calibration of this prognostic model. However, discrimination ability in our cohort is poor, which suggests that we cannot implement this model in our clinical practice. Therefore, it would be desirable to perform new studies that aim to recalibrate the IMPACT score and studies that evaluate the clinical or prognostic influence of its widespread use before applying it into daily organ allocation decision-making.

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CONFLICTS OF INTEREST

The authors declare that they have no relevant conflicts of interest to disclosure with regard to the current project.

AUTHORSHIP CONTRIBUTION STATEMENT

Carlos Ortiz-Bautista: Concept/design, data collection, data interpretation, manuscript drafting, critical revision of article, approval of article. Javier Muñiz: research design, data analysis/interpretation, critical revision of article, approval of article. Luis Almenar-Bonet, María G. Crespo-Leiro, José M. Sobrino-Márquez, Marta Farrero-Torres, María D. García-Cosio, Beatriz Díaz-Molina, Francisco González-Vilchez, Amador López Granados, Manuel Gómez-Bueno, Luis de la Fuente-Galán, Teresa Blasco-Peiró, Gregorio Rábago Juan-Aracil, Luis García-Guereta: critical revision of article, approval of article. Isabel Zegrí-Reiriz, Zorba Blázquez-Bermejo, Iris P. Garrido-Bravo, Elena García-Romero: data collection, critical revision of article, approval of article. Juan F. Delgado-Jiménez: Concept/design, critical revision of article, approval of article.

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TABLE 1. Variables included in the IMPACT score

Recipient variable	Assigned points
Age > 60 years	3
Female sex	3
Raza	
Caucasian/Hispanic/Other	0
African American	3
Bilirubin (mg/dl)	
0–.99	0
1–1.99	1
2–3.99	3
≥4	4
Creatinine clearance (ml/min)[a]	
≥50	0
30–49	2
<30	5
Heart failure etiology	
Idiopathic	0
Other	1
Ischemic	2
Congenital	5
Dialysis pre-transplant	4
Recent infection	3
Mechanical ventilation pre-transplant	5
Intra-aortic balloon pump	3
Temporary mechanical circulatory support[b]	7
Ventricular assist devices	
HeartMate II	0
Older-generation pulsatile[c]	3
Newer-generation continuous excluding HeartMate II[d]	5
Total points possible	50

[a] Cockcroft-Gault formulae: {[140-age (years)] × weigh (kg)/[72 × serum creatinine (mg/dl)]} × (.85 in women).

[b] ECMO, Abiomed BVS 5000, BioMedicus, Levitronix, TandemHeart, Impella.

[c] BerlinHeart EXCOR, Abiomed BV 5000, HeartMate I, XE y XVE, ThoratecIVAD, Toyobo, Novacor, Medos y LionHeart.

[d] HeartWare, Jarvik, MicroMed-DeBakey y VentrAssit.

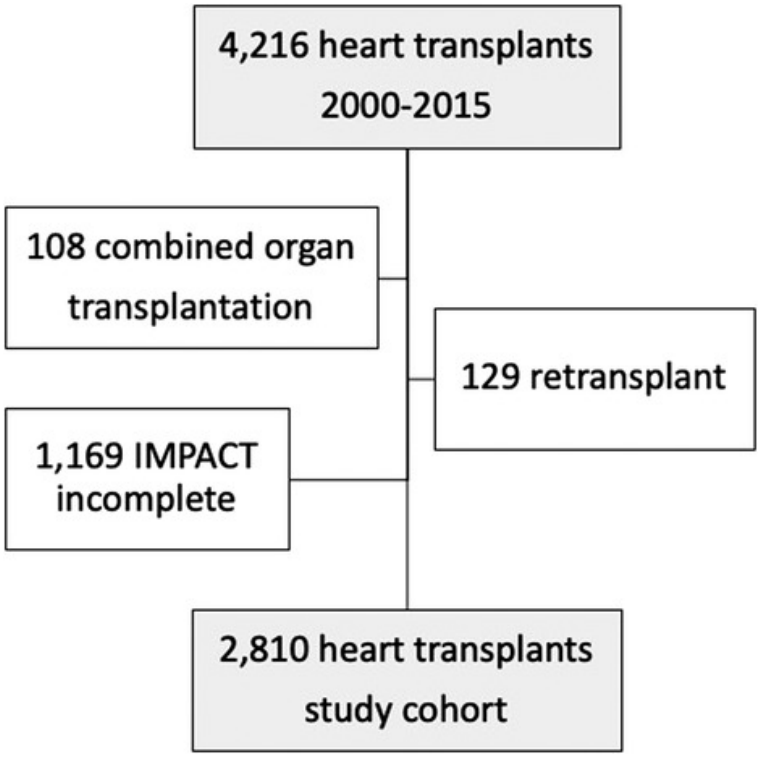

FIGURE 1. Flow chart of the selection of the study cohort. Of the 1169 patients excluded due to missing values 1164 were excluded due to missing creatinine or bilirubin value and five patients due to missing weigh value to calculate the creatinine clearance

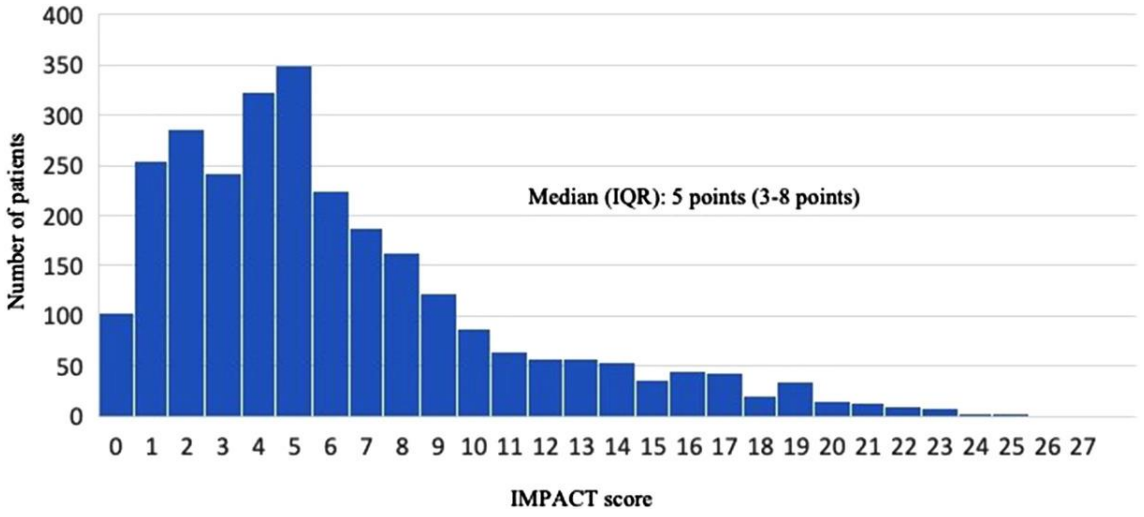

FIGURE 2. Distribution of the IMPACT score in the study cohort. IQR, interquartile range

TABLE 2. Baseline characteristics of the final cohort (*N* = 2.814)

Variable	Cohort
Age (years), mean ± SD	52.8 ± 11.6
Male sex, *n* (%)	2.202 (78.4)
Race	
Caucasian, *n* (%)	2.798 (99.6)
African American, *n* (%)	12 (.4)
Serum bilirubin (mg/dl), median (IQR)	1 (.64, 1.64)
Creatinine clearance (ml/min)[a], median (IQR)	74.02 (56.2, 96.7)
Heart failure etiology	
Idiopathic, n (%)	794 (28.2)
Ischemic, n (%)	1167 (41.5)
Congenital, n (%)	71 (2.5)
Other, n (%)[f]	778 (27.7)
Dialysis prior to HT[b], *n* (%)	42 (1.5)
Recent infection, *n* (%)	370 (13.2)
Pre-transplant mechanical ventilation, n (%)	383 (13.6)
Mechanical circulatory support	
No, *n* (%)	2.059 (73.3)
Intraaortic balloon pump, *n* (%)	430 (15.3)
Temporary mechanical circulatory support[c], *n* (%)	282 (10)
Continuous ventricular assist devices[d], *n* (%)	6 (.2)
Pulsatile ventricular assist devices[e], *n* (%)	33 (1.2)

Abbreviations: IQR, interquartile range; HT, heart transplant; SD, standard deviation.

[a] Cockcroft-Gault formula: {[140-age (years)] × weigh (kg)/[72 × serum creatinine (mg/dl)]} × (.85 if female).

[b] Any type of renal replacement therapy at the time of HT.

[c] ECMO, Abiomed BVS 5000, BioMedicus, Levitronix, TandemHeart, Impella.

[d] HeartWare, HeartMate II, HeartMate 3, Jarvik, MicroMed-DeBakey y VentrAssit.

[e] BerlinHeart EXCOR, Abiomed BV 5000, HeartMate I, XE y XVE, ThoratecIVAD, Toyobo, Novacor, Medos y LionHeart.

[f] See Supplementary Table S1.

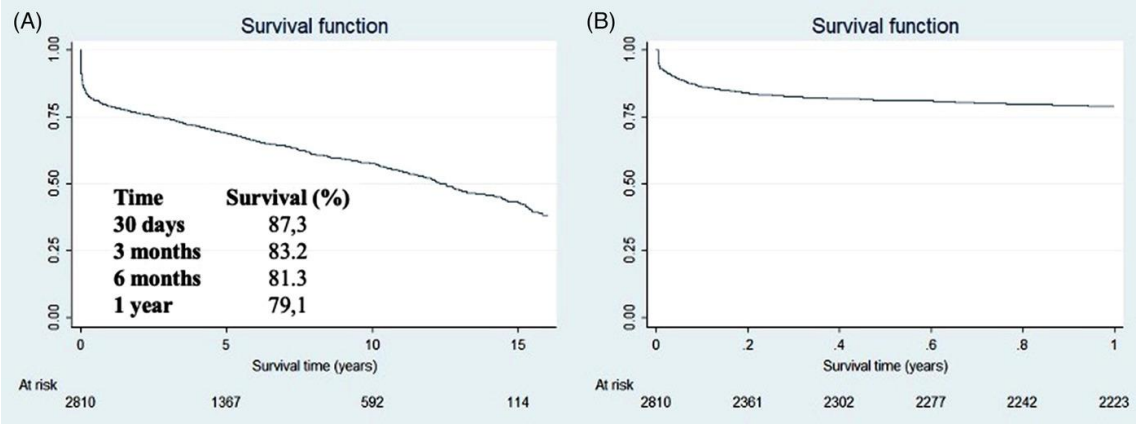

FIGURE 3. (A) Kaplan-Meier cumulative overall survival. (B) Kaplan-Meier cumulative 1-year survival

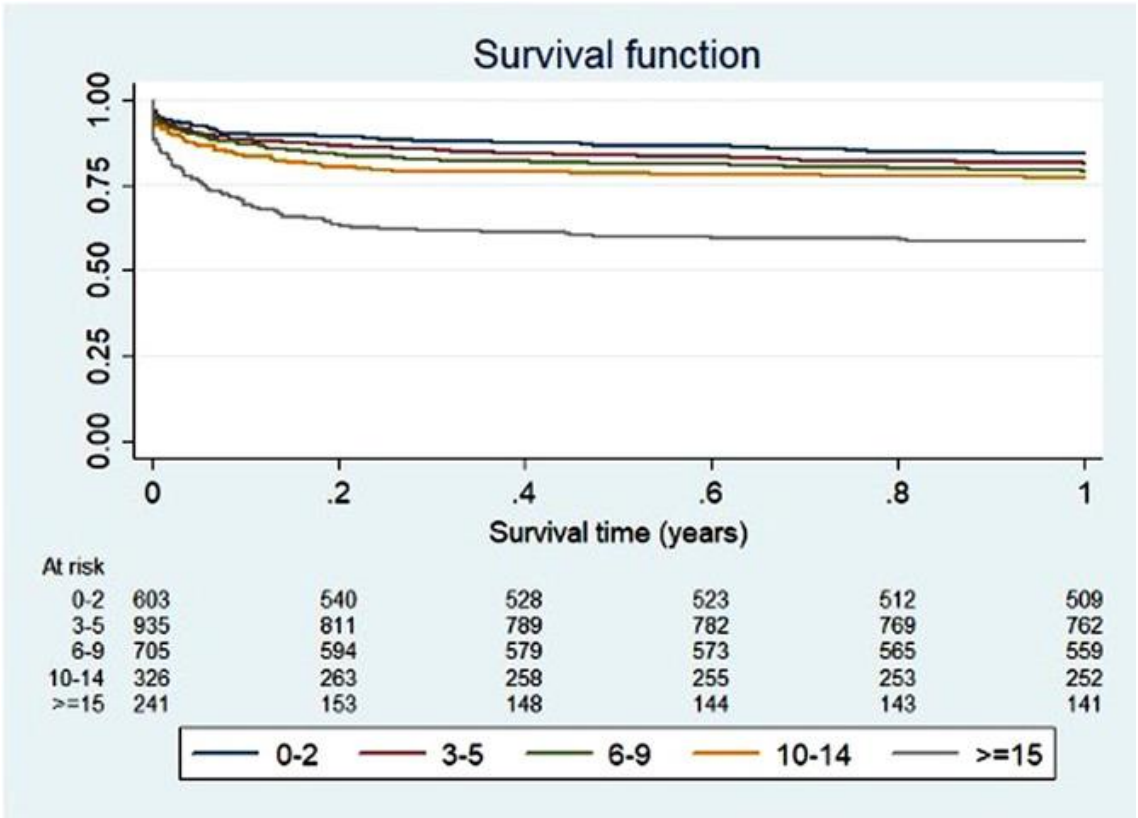

FIGURE 4. Kaplan-Meier cumulative 1-year survival as stratified by different IMPACT score categories

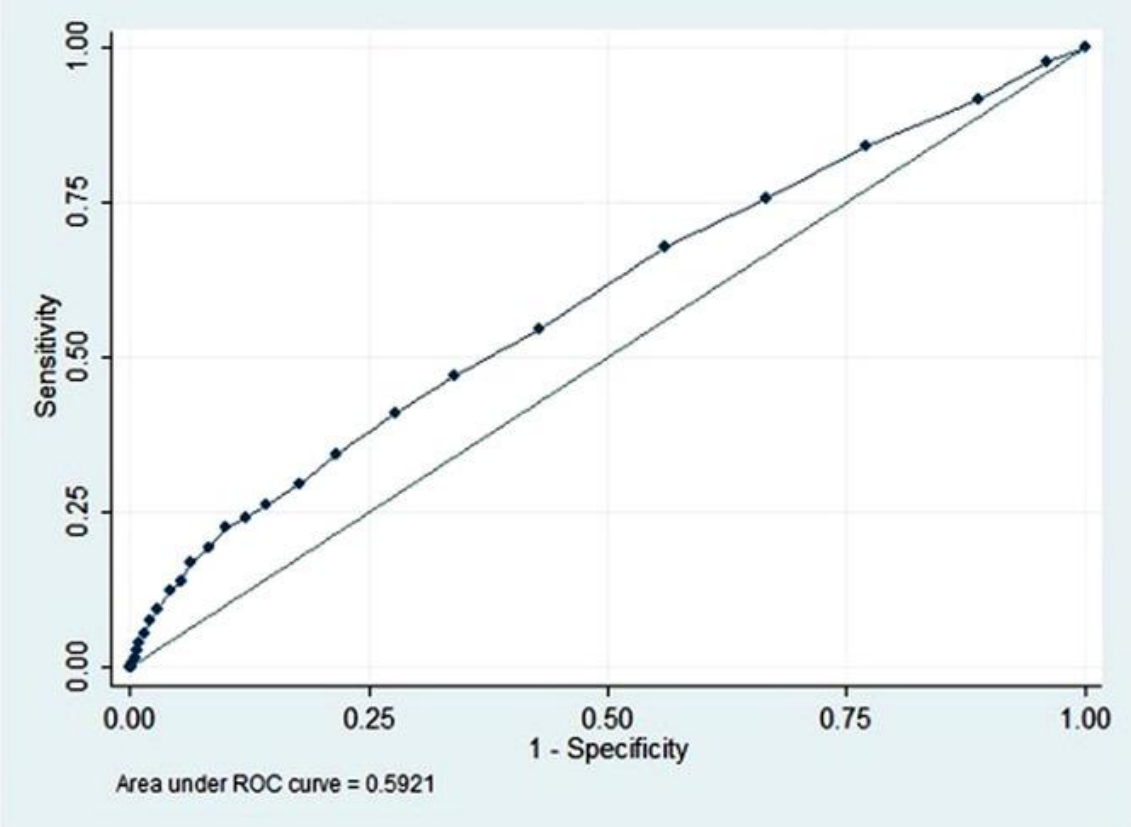

FIGURE 5. Discrimination ability of the IMPACT score in the study cohort. AU-ROC = area under the receiver-operating curve