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Original Research

Phase I prognostic online (PIPO): A web tool to improve patient selection for oncology early phase clinical trials

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Abstract ***Purpose:*** Patient selection in phase 1 clinical trials (Ph1t) continues to be a challenge. The aim of this study was to develop a user-friendly prognostic calculator for predicting overall survival (OS) outcomes in patients to be included in Ph1t with immune checkpoint inhibitors (ICIs) or targeted agents (TAs) based on clinical parameters assessed at baseline.
Methods: Using a training cohort with consecutive patients from the VHIO phase 1 unit, we constructed a prognostic model to predict median OS (mOS) as a primary endpoint and 3-month (3m) OS rate as a secondary endpoint. The model was validated in an internal cohort after temporal data splitting and represented as a web application.
Results: We recruited 799 patients (training and validation sets, 558 and 241, respectively). Median follow-up was 21.2 months (m), mOS was 10.2 m (95% CI, 9.3–12.7) for ICIs cohort

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and 7.7 m (95% CI, 6.6–8.6) for TAs cohort. In the multivariable analysis, six prognostic variables were independently associated with OS – ECOG, number of metastatic sites, presence of liver metastases, derived neutrophils/(leukocytes minus neutrophils) ratio [dNLR], albumin and lactate dehydrogenase (LDH) levels. The phase 1 prognostic online (PIPO) calculator showed adequate discrimination and calibration performance for OS, with C-statistics of 0.71 (95% CI 0.64–0.78) in the validation set. The overall accuracy of the model for 3m OS prediction was 87.2% (95% CI 85%–90%).

Conclusions: PIPO is a user-friendly objective and interactive tool to calculate specific survival probabilities for each patient before enrolment in a Ph1t. The tool is available at https://pipo.vhio.net/.

1. Introduction

Patient selection in phase I clinical trials continues to be a challenge in the era of immune checkpoints inhibitors (ICIs) and combinations with small molecules or targeted agents (TAs). Furthermore, phase 1 trialists are more frequently dealing with novel compounds and new trial designs with large expansion cohorts [1], looking for preliminary evidence of anti-tumour activity and safety in different tumour types and disease settings. In fact, during these last years, certain phase 1 trials have had registrational value transforming the classical drug development path. Despite these trends, patients recruited in phase 1 trials are mostly refractory to standard-of-care therapies. Paradoxically, participation in phase 1 trials requires a minimum required life expectancy and a lack of significant symptoms. The need to balance the potential risks of toxicity and benefits of investigational drugs in this particularly vulnerable cancer population is critical. Moreover, keeping in mind that the primary objective of phase 1 studies is to evaluate the safety profile and to identify the maximum tolerated dose [2], with response rates lower than 20% on average in non-molecularly guided clinical trials [3,4]. Most phase 1 clinical trials use the life expectancy of at least 3 months as a specific inclusion criterion to minimise the chances of clinical deterioration during the dose-limiting toxicity (DLT) assessment period. Nevertheless, there is no consensus on how to objectively make this estimation in real practice.

Several prognostic scores have been developed for phase 1 trials. Most are based on overall survival (OS) prediction but not in the specific timepoint of survival rate at 3 months (3m). These scores were developed for patients treated with cytotoxic agents or targeted drugs in phase 1 units of the Royal Marsden Hospital (RMH score) [5] and the MD Anderson Cancer Center (MDACC) [6]. More recently, prognostic scores specifically for ICIs have been designed at Gustave Roussy Hospital, Paris, France, (GRIm-Score) [7] or MDACC (MDA-ICI) [8]. However, none of them were initially developed using patients treated with both TAs and ICIs. Regardless, if these scores are prognostic but not predictors, there should be no significant differences when stratifying for treatment type. This was, in fact, demonstrated in advanced non-small cell lung cancer (NSCLC) population with Lung Immune Prognostic Index (LIPI) [9], which has been validated as a prognostic score not only for ICIs but also chemotherapy and TAs [10]. One additional important limitation of all published prognostic scores is that continuous and ordinary variables are dichotomised using a specific cut-off point for simplification purposes, which may reduce the performance of the model when applied in real life [11].

The main objective of this study was to develop an online prognostic calculator for patients with refractory advanced solid tumours potentially eligible for phase 1 clinical trials that (i) was independently useful for both ICIs and TAs; (ii) explored continuous and ordinary variables without dichotomisation; and (iii) robustly estimated OS and life expectancy at 3m. Finally, we wanted to develop a user-friendly online decision support tool to facilitate clinical application.

2. Patients and methods

2.1. Patients and data collection

We analysed data from patients recruited in phase 1 clinical trials of the Vall d'Hebron Institute of Oncology (VHIO) between January 2011 to March 2020. The ICI cohort included 518 patients treated with any ICI drug as monotherapy or in combination with other immunotherapeutic agents (n = 518), while the TAs cohort included 281 patients treated with single agents and combinations with other targeted drugs not considered Tier 1 in the ESMO scale of clinical actionability for molecular targets (ESCAT)-[12]. All patients received at least one dose of the experimental compounds.

We retrospectively collected 18 variables from the electronic medical record, which included patient demographics (age and sex), clinical-pathological variables

(tumour type, number of metastatic sites, specific sites with metastases), laboratory parameters at study entry (lymphocyte count, neutrophil count, derived neutrophils/[leukocytes minus neutrophils] ratio [dNLR], platelets count, albumin and LDH), treatment regimens (monotherapy or combinations), radiological endpoints such as tumour assessment by RECIST 1.1, and survival outcomes (OS and 3m survival rate). We also calculated the different prognostic scores for each patient: RMH, GRIm, LIPI, MDACC and MDA ICI for both groups (TAs and ICIs).

Following the TRIPOD guideline [13], we performed a temporal data splitting to create a validation set. The first 70% recruited patients were included in the training set (n = 558) after balancing for ICIs and TAs treatment. And the last 30% recruited patients were included in the validation set (n = 241).

All procedures followed were in accordance with the ethical standards of the responsible committee on human research (institutional and national) and with the Helsinki Declaration of 1964 and later versions. This study was approved by the institutional review board of Vall d'Hebron University Hospital with a waiver of informed consent.

2.2. Statistical methods

Our primary endpoint was OS, calculated from the date of phase 1 first dose until the date of death from any cause. Univariate Cox proportional hazard (PH) models were fitted in the training set without dichotomising ordinary or continuous factors. In order to select variables with the highest prognostic impact in OS, we performed a least absolute shrinkage and selection operator (LASSO) regression using package *glmnet* in R software to build the most parsimonious multivariate model. A multivariable stratified Cox model was fitted with the selected variables and using the treatment cohort (ICIs versus TAs) as a stratification factor, allowing a different baseline hazard function for each treatment type. We investigated (i) significant interactions between the selected variables and (ii) differences in the estimation by treatment cohort ($P < 0.05$ according to ANOVA test). For illustration purposes, continuous covariates were dichotomised based on previously reported cut-off points to generate Kaplan–Meier curves comparing patients with different risk scores.

We built an R Shiny app to create the phase 1 prognostic online (PIPO) tool. In the prognosis calculator, we relaxed the linearity assumption for continuous predictors using restricted cubic splines by means of the *rms* R package [14]. Using the estimated coefficient in the multivariate Cox model, adjusted Kaplan–Meier curves can be calculated with patient-specific information. To validate the tool, we assessed the discrimination and calibration performance of the model [15]. We performed an internal bootstrap validation in the training set to evaluate optimism in the predictions (resampling of 1000 iterations), and calibration plots were calculated for different survival time points. Harrell's C-statistic was calculated to determine the discrimination capacity of the proposed model in the validation set.

Additionally, using multiple permutations, we calculated the relative proportion of explained variation in OS that was accounted for the selected prognostic factors (*survMisc* R package) [16]. The median follow-up was calculated using Kaplan–Meier reverse method. Imputation of random missing values was carried out via the *mice* R package. All analyses were performed using R statistical software version 3.6.2.

3. Results

3.1. PIPO tool

From January 2012 to March 2020, 799 patients with different tumour types treated at the VHIO phase 1 unit fulfilled the inclusion criteria for study participation (Fig. A1). Baseline patient characteristics are summarised in Table 1, Tables A1 and A2. The median follow-up was 21.2 months (m). Median OS (mOS) was 10.2 m (95% CI, 9.3–12.7) for the ICIs cohort and 7.7 m (95% CI, 6.6–8.6) for the TAs cohort.

Fig. 1 describes univariate and multivariate Cox models for OS in the training set. The most parsimonious OS multivariate model included the followed prognostic factors assessed at baseline: ECOG performance status, number of metastatic sites, liver metastases, derived neutrophils/(leukocytes minus neutrophils) ratio [dNLR], albumin and lactate dehydrogenase (LDH) levels. Separately, results by treatment cohorts can be found in Table A3. No difference was found in HR estimations between ICIs and TAs cohorts (ANOVA test, all p-value >0.05). Fig. 2A illustrates the relative contribution of each factor in the OS prediction; factors with the most explained variation in the multivariable model were the number of metastatic sites (28%) and albumin (26.5%). Fig. 2B shows the shape of the association between selected factors and OS risk after relaxing the linearity assumption for continuous variables.

All the selected factors were combined to develop a prognostic tool for patients treated in early trials, Phase 1 prognostic online (**PIPO**): https://pipo.vhio.net/. PIPO is an interactive tool to calculate specific survival probabilities for each patient before enrolment in a

phase 1 trial. End-users can easily see the impact of the six clinical-pathological and laboratory variables for prognostication in terms of KM survival curves and time-point estimates, including 95% CI. Variable are treated as dichotomous, ordinal or continuous when appropriate. Table A4 details the final model estimation.

3.2. PIPO score

For illustration purposes, we analysed dichotomised ordinal and laboratory variables. We classified patients into prognostic groups based on the number of risk factors (scores from 0 to 6, see Fig. A2). The prognostic score showed a clear association with OS in the training set (Fig. A3). Finally, the score was divided into three groups in order to facilitate results interpretation: (1) good prognosis (0–2 points), (2) intermediate prognosis (4–5 points) and (3) poor prognosis (5–6 points). These three groups showed major differences in OS (Fig. 3A). In the good prognosis group, the mOS was 16.3 months; in the intermediate mOS was 6.6 m (HR 2.21, [95% CI 1.79–2.72]; $p < 0.001$) and in the poor prognostic group mOS was 2.9 m (HR 4.90, [95% CI 3.59–6.68]; $p < 0.001$).

Additionally, we evaluated the PIPO score prognostic impact separately in the ICIs and the TAs cohort. In the ICIs cohort, the prognostic groups showed an mOS of 17.6m (95% CI 14–24.3), 6.3m (95% CI 5.7–7.5) and 3.8m (95% CI 2.5–7.9), respectively. While in the TAs cohort, the mOS estimation was 14.7m (95% CI 10.3–19.3), 7.1m (95% CI 5.9–8.6) and 2.7m (95% CI 2.4–3.5), respectively (Fig. 3B and C). The difference in OS between prognostic score groups was again independent of treatment type (ANOVA test, p-value >0.05).

Next, we validated existing prognostic scores (RMH, MDACC, LIPI, GRim, MDA-ICI) in both populations (ICIs and TAs), showing a satisfactory OS predictive capacity independently of treatment type (Fig. A4).

3.3. Model validation

In order to ensure the performance of the model, we assessed the discrimination and calibration of the PIPO tool in the training set (n = 558). The C-statistic of the training was 0.71 (95% CI 0.68–0.74), at bootstrap resampling set C = 0.70, for a total optimism of 0.01. We then created a series of calibration plots for different time points to compare predicted probabilities and observed probabilities (Fig. 4).

After assessing the performance, we evaluated the model in the validation set (n = 241). In the good prognosis group the mOS was 14.4m, in the intermediate group was 6.3 m (HR 3.36, [95% CI 2.08–5.43]; $p < 0.001$) and in the poor prognostic group was 2.4 m (HR 10.1, [95% CI 4.45–23]; $p < 0.001$) [Fig. 2B].

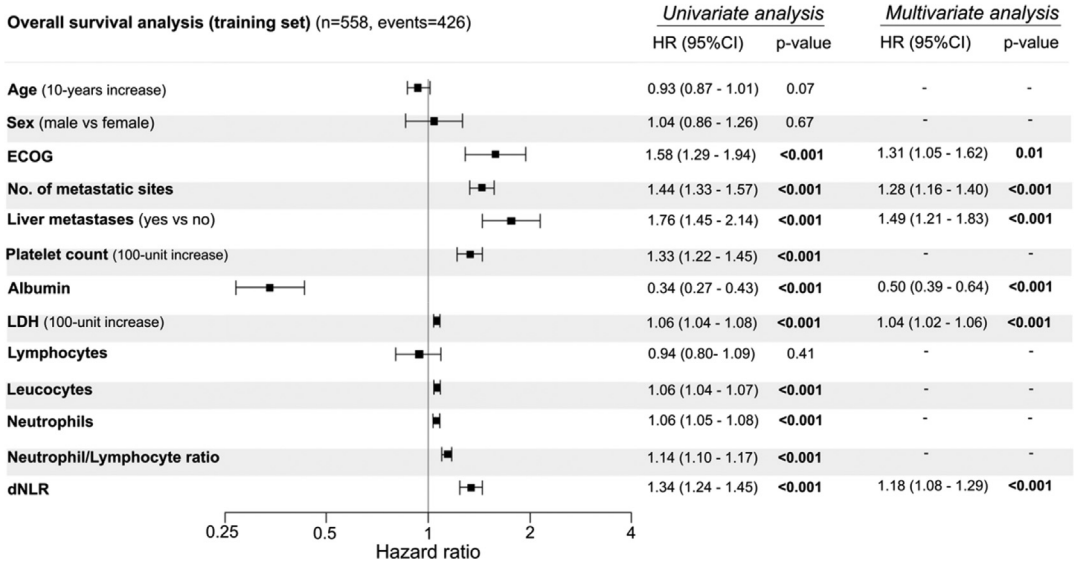


Fig. 1. **Cox models for overall survival in the training set** The LASSO regression was performed to select the factors to be included in the most parsimonious multivariate model. The multivariate model was stratified by treatment type (ICIs versus TAs). ECOG, performance status; LDH, lactate dehydrogenase; dNRL, derived neutrophils/(leukocytes minus neutrophils) ratio; HR, hazard ratio; CI, confidential interval.

Table 1
Study population characteristics.

		All patients	Training cohort	Validation cohort
Total, n (%)		799 (100)	558 (70)	241 (30)
Age years, median (IQR)		59.4 (50.2–67.4)	59.7 (49.2–67.3)	59.2 (51.9–67.8)
Sex, female		413 (51.7)	278 (49.8)	135 (56.0)
Tumor type	Breast	95 (11.9)	57 (10.2)	38 (15.8)
	CRC	134 (16.8)	76 (13.6)	58 (24.1)
	Non-CRC gastrointestinal	136 (17)	94 (16.8)	42 (17.4)
	Gynaecological	76 (9.5)	47 (8.4)	29 (12)
	H&N	55 (6.9)	39 (7)	16 (6.6)
	Lung	83 (10.4)	71 (12.7)	12 (5)
	Melanoma	94 (11.8)	79 (14.2)	15 (6.2)
	Others	126 (15.8)	95 (17)	31 (12.9)
ECOG, 0		315 (39.4)	206 (36.9)	109 (45.2)
Treatment				
Monotherapy		430 (53.8)	307 (55.0)	123 (51.0)
Combination		369 (46.1)	251 (44.9)	118 (48.9)
No. metastatic sites				
Median (IQR)		3 (2–3)	3 (2–3)	3 (2–4)
No. metastatic sites > 2		404 (50.6)	281 (50.4)	123 (51.0)
Liver metastases		354 (44.3)	234 (41.9)	120 (49.8)
Platelet				
Median (IQR)		259 (194–325)	260 (200–329)	254 (189–317)
Platelet > 400		105 (13.2)	75 (13.5)	30 (12.6)
Albumin				
Median (IQR)		4 (3.7–4.2)	4 (3.7–4.2)	4 (3.7–4.3)
Albumin < 3.5		106 (13.3)	84 (15.0)	22 (9.1)
LDH				
Median (IQR)		442 (349–631)	441 (349–622)	449 (349–644)
LDH > ULN		534 (66.8)	373 (66.8)	161 (66.8)
Lymphocytes				
Median (IQR)		1.3 (1–1.7)	1.3 (0.9–1.7)	1.4 (1.1–1.8)
Lymphocytes < 1.2		291 (36.4)	229 (41.0)	62 (25.7)
Leucocytes				
Median (IQR)		6.7 (5.2–8.5)	6.5 (5.1–8.6)	7 (5.5–8.3)
Leucocytes > 11		73 (9.1)	58 (10.4)	15 (6.2)
Neutrophils				
Median (IQR)		4.3 (3.3–5.9)	4.3 (3.3–5.9)	4.4 (3.4–5.9)
Neutrophils > 7		115 (14.4)	88 (15.8)	27 (11.2)
Neutrophil/Lymphocyte ratio				
Median (IQR)		3.4 (2.4–4.9)	3.4 (2.5–5)	3.2 (2.3–4.7)
Neutrophil/lymphocyte > 6		121 (15.1)	85 (15.2)	36 (14.9)
dNLR				
Median (IQR)		2.1 (1.5–2.7)	2.1 (1.6–2.8)	1.9 (1.5–2.5)
dNLR > 3		151 (18.9)	108 (19.4)	43 (17.8)

N, number; IQR, interquartile range; CRC, colorectal, H&N, head and neck; ECOG, performance status; LDH, lactate dehydrogenase; dNRL, derived neutrophils/(leukocytes minus neutrophils) ratio HR.

Overall, the C-statistics in the validation set was 0.71 (95% CI 0.64–0.78).

3.4. Objective measurement of life expectancy at 3 months

To evaluate the model capacity with the PIPO tool to detect deaths within 3 months, we first assess the performance of the three prognostic groups in the validation set. Fifty per cent of patients with a poor prognosis score (5–6 points) die before 3 months, 18.7% in the intermediate score and only 4.7% in the good prognostic score (Fig. 3B).

PIPO tool is also able to estimate the individual probability of death at 3 months with 95% CI. When the 3m OS rate was less than 60%, we considered that the patient had a low life expectancy, and therefore, would not have fulfilled inclusion/exclusion criteria for the phase 1 clinical trial. We tested each patient with a follow-up of at least 3 months in the pooled cohort (749 out of 799), using the cut-off of 60% as described above and compared it with real survival data at the same

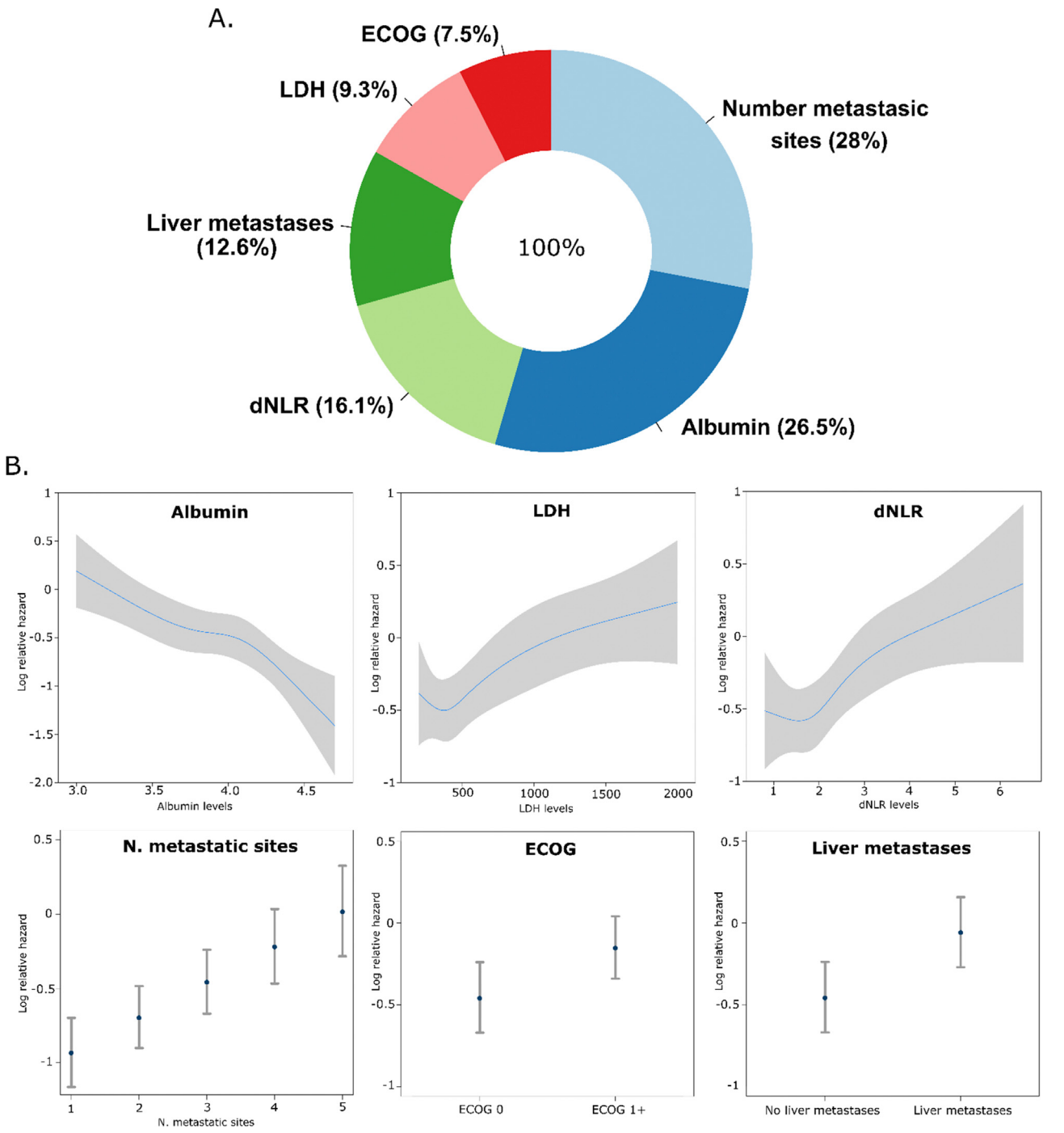


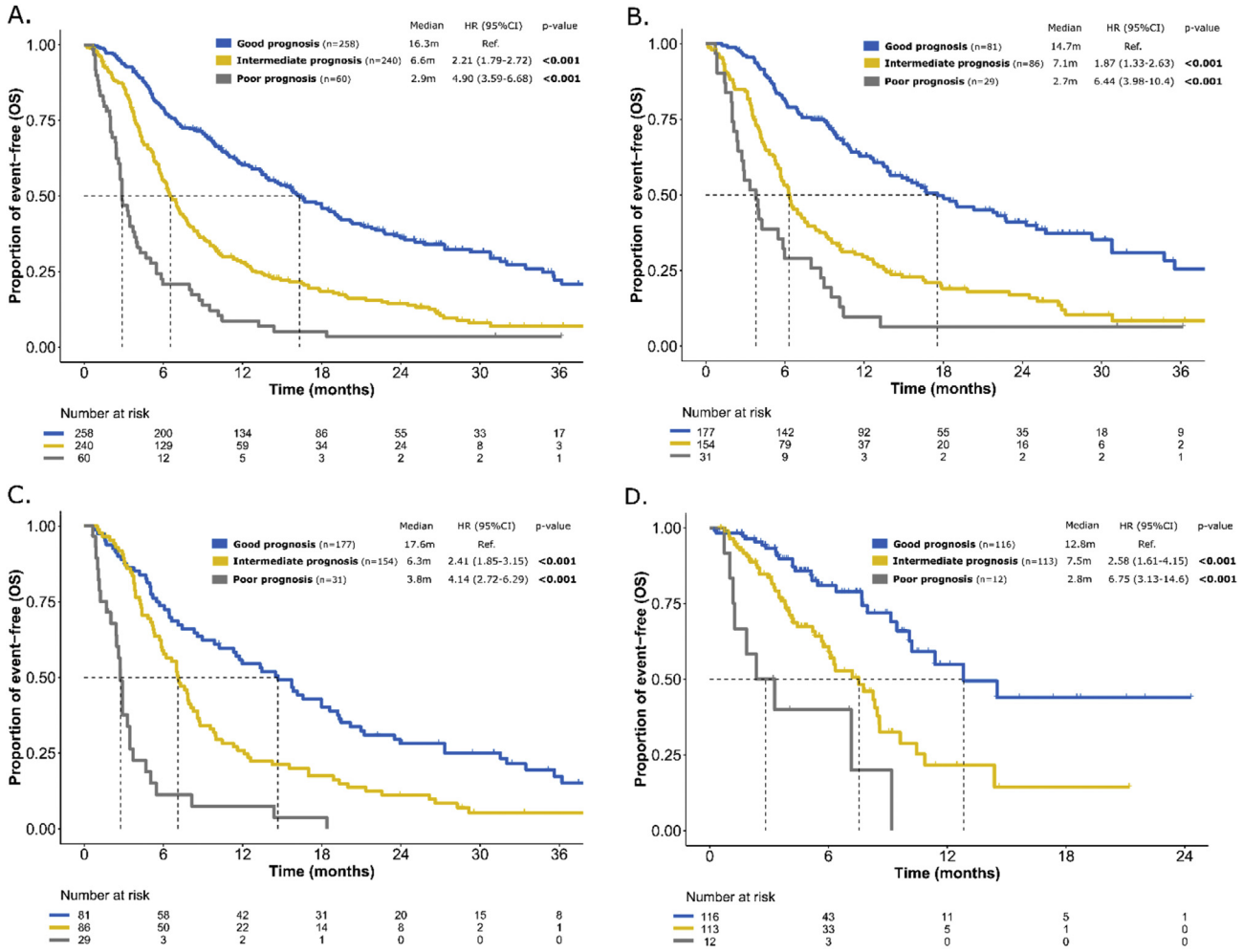
Fig. 2. Impact of clinical variables on PIPO tool. A. Relative contribution of each factor in the overall survival prediction. B. Shape of association between selected factors and overall survival risk after relaxing the linearity assumption for continuous variables. ECOG, performance status; LDH, lactate dehydrogenase; dNRL, derived neutrophils/(leukocytes minus neutrophils) ratio; HR, hazard ratio; CI, confidential interval.

time-point. The overall accuracy for 3m OS prediction was 87.2% (95% CI 85%–90%), and the area under the precision-recall curve was 95.4% (95% CI 93%–97%). The specificity was 98.6% (95% CI 98%–99%), with only 8 out of 31 (25.8%) patients predicted to have a life expectancy <3 months living longer than 3 months. The sensitivity was 20.9% (95% CI 14%–29%), with 23 out of 110 patients that died within the first 3m being correctly identified. The positive predicted value was 74.2% (95% CI 55%–88%), 23 out of the 31 patients labelled as high risk of dying within 3 months having an early death.

4. Discussion

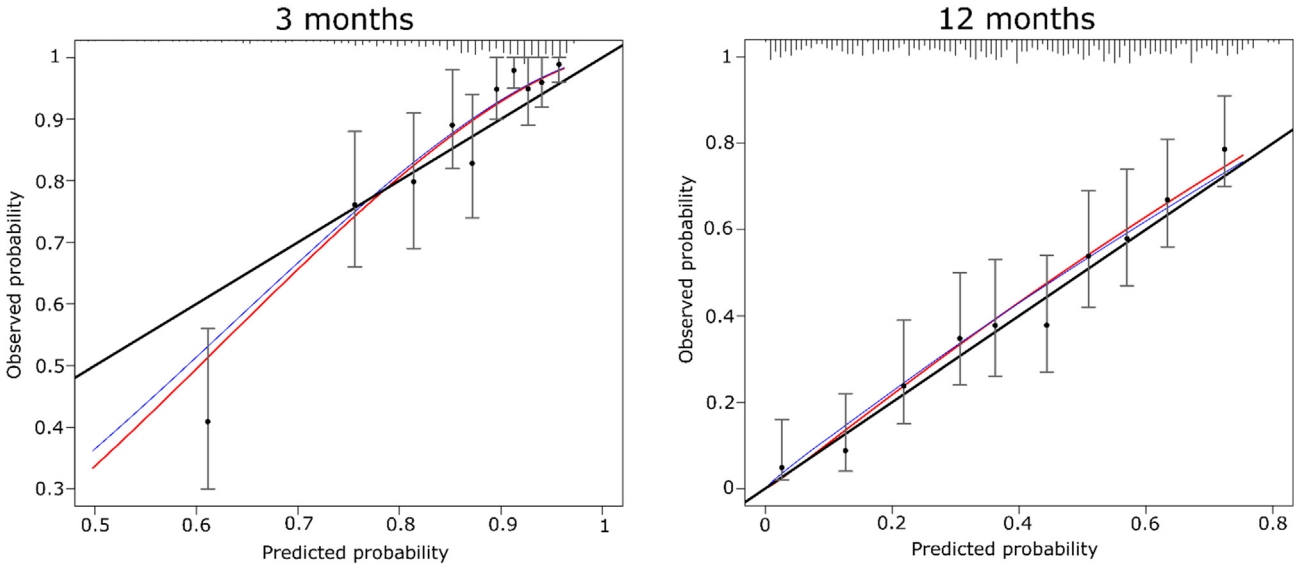
The ability to improve patient selection in phase 1 clinical trials is crucial for all stakeholders in drug development: patients, clinicians, pharmaceutical companies and regulatory agencies. The main objectives of this selection are [1]: minimise the potential for toxicity and worsening the quality of life of participating patients; and [2] obtaining solid, robust and reproducible data regarding the safety and efficacy profile of the compound to aid in further drug development. With this purpose having a life expectancy of at least 3 months is a universally accepted criterion in phase 1 trials. However, the capability to predict survival is a challenge, and this criterion remains mostly a clinical "best guess". The current study describes the development and validation of the phase 1 prognostic online (PIPO) tool. With 518 patients treated with ICIs in phase 1 trials, it is the largest series published with this objective and also the first tool developed and validated for both ICIs and TAs in phase 1 trials independently.

The PIPO tool is built on objective clinical and analytical parameters: ECOG, number of metastatic sites, presence of liver metastases, dNLR, albumin and LDH levels. All these variables were tested in the univariate and multivariate analysis of the training set with the overall population (Fig. 1, n = 558) and separately by treatment type (Table A3; ICIs = 362 and TAs = 196), maintaining their impact in OS, with the exception of ECOG status in TAs population. Of note, all patients participated in phase 1 trials, so their ECOG at the time of study entry was mostly 0 or 1. It has been demonstrated that the LIPI score works as a discriminatory prognostic index in patients treated with chemotherapy or TAs [17]. Here, we tested the ICIs scores in the TAs population and vice-versa (Fig. A4), showing that their prognostic roles are independent of treatment modality, in line with their prognostic and



Association between the prognostic score and overall survival (OS) in A) the overall training cohort (n=558), B) patients treated with ICIs in the training cohort (n=362), C) patients treated with TAs in the training cohort (n=196) and D) the validation cohort (n=241).

Fig. 3. OS analysis using PIPO score.



Calibration plots in the training set at 3 and 12 months. X-axis shows average predicted probability values for each decile, and y-axis shows corresponding observed probability in each decile. Error bars represent 95% confidence intervals of mean predicted probabilities. The black line represents the perfect calibration. The red curve represents the observed curve for the overall model using a flexible adaptive hazard regression approach and the blue curve represent the corrected estimation for overfitting, allowing estimation of the likely future calibration performance.

Fig. 4. Calibration plots.

non-predictive nature. For this reason, the PIPO tool was developed and is useful for both treatment types.

All PIPO parameters have been reported previously as important prognostic factors and included in several prognostic indexes [5,6,8,9]. In fact, the PIPO tool is based on combining parameters of different scores: RMH criteria (number of metastatic sites, albumin and LDH levels), LIPI criteria (dNLR and LDH levels) plus ECOG and presence of liver metastases. The novelty of the PIPO tool relies on two important considerations. First, in all of these indexes, ordinary variables are dichotomised using a specific cut-off point. For example, an LDH value above the upper normal limit (UNL) is assigned with 1 point, and normal values with 0 in the classic scores [5,7,9]. The price to pay for this simplification is a substantial loss in prognostic information. Continuing with the same example, it would grade with the same score two patients with very different LDH levels such as 1.1 × UNL or 10 × UNL (1 point) and differently for two patients with similar values around the cutoff point such as 0.9 × UNL and 1.1 × UNL (0 and 1 point respectively). PIPO prognostic tool uses all available information with no simplification to better adjust the prognostic model. The second important aspect to highlight is that the PIPO tool provides a patient-specific risk prediction for any given time point; instead of assigning patients to a predetermined risk group where estimation of the individual risk is compromised.

To our knowledge, the PIPO tool is the first prognostic model estimating a specific probability of early death (before 3 months after enrollment) for each patient in phase 1 trials. As stated before, this parameter is a universal inclusion criterion in drug development studies; however, its evaluation is completely subjective and based on the clinical experience of the physician. All patients in this study met the eligibility criteria for each specific trial in which they were included; despite this, 110 patients out of 749 with enough follow-up died in the first 3 months (14.6%). Using the PIPO tool to evaluate a 3m OS rate of less than 60%, our specificity was high (98.6%) with good overall accuracy (87.2%) and precision-recall (95.4%). However, sensitivity was low (20.9%), indicating PIPO was not able to capture early deaths in multiple cases, as they may be due to several causes such as toxicity, infections or even hyperprogression with ICIs, which are not detected by prognosis factors [18]. However, the specificity and the positive predictive value reflect the fact that when the model detects a potential early death, it will be very likely to observe the patient's death within the first 3 months.

Our study has some limitations. First, although the data were collected prospectively in patients participating in phase I clinical trials, the analysis is retrospective and conducted in a single institution. PIPO prognostic model has been internally validated; however, an additional external prospective validation is recommended. Second, both the training and validation cohorts include multiple tumour types and different treatment regimens both as monotherapy and in combination; this heterogeneity might potentially influence the survival results, despite the adjustments made in the multivariate analysis. However, we believe that our

diverse cohort represents the real-world population of phase 1 trial patients, and the PIPO web application will facilitate external validation by other institutions.

In conclusion, the PIPO tool is a user-friendly calculator risk to prognosticate survival events in patients involved in phase 1 trials, independently of the treatment type. Based on a combination of ordinary classic prognostic factors without dichotomisation, the model allows for a patient-specific prediction. PIPO tool is able to help the physician in the decision-making process, evaluating patients in phase 1 trials and supporting their decisions; the tool is available at https://pipo.vhio.net/.

Author contributions

IM: study design, patient recruitment, data collection, data analysis, data interpretation, manuscript writing, manuscript review, supervision. **GV**: study design, data analysis, data interpretation, manuscript writing, manuscript review, software. **CH**: study design, patient recruitment, data collection, data analysis, data interpretation, manuscript review. **JML**: study design, patient recruitment, data collection, data analysis, data interpretation, manuscript writing, manuscript review. **RB**: study design, data collection, data analysis, data interpretation, manuscript writing, software. **AP:** software. **IB:** patient recruitment, data collection, data analysis, data interpretation. **AA**: patient recruitment, data collection, data analysis, data interpretation. **VB**: patient recruitment, data collection, data analysis, data interpretation. **MOA**: patient recruitment, data collection, data analysis, data interpretation. **JV**: patient recruitment, data collection, data analysis, data interpretation. **CV**: data collection, **EMC**: data collection, data analysis, data interpretation, manuscript writing, manuscript review **EE**: data collection, data analysis, data interpretation, manuscript writing, manuscript review **JR**: data collection, data analysis, data interpretation, manuscript writing, manuscript review **CS**: study design, patient recruitment, data collection, data analysis, data interpretation, manuscript writing, manuscript review **TM**: study design, patient recruitment, data collection, data analysis, data interpretation, manuscript writing, manuscript review **AO**: data collection, data analysis, data interpretation, manuscript writing, manuscript review **JC**: data collection, data analysis, data interpretation, manuscript writing, manuscript review **EF**: data collection, data analysis, data interpretation, manuscript writing, manuscript review **JT**: patient recruitment, data analysis, data interpretation, manuscript writing, manuscript review **RD**: study design, patient recruitment, data collection, data analysis, data interpretation, manuscript writing, manuscript review **EG**: study design, patient recruitment, data collection, data analysis, data interpretation, manuscript writing, manuscript review, supervision.

Conflict of interest statement

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Appendix A. Supplementary data

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