Zare and Feizi *BMC Palliative Care* (2024) 23:220
https://doi.org/10.1186/s12904-024-01550-z

BMC Palliative Care

RESEARCH

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Predicting place of death of patients with advanced cancer receiving home-based palliative care services in Iran

Mohammad-Sajad Zare[1] and Awat Feizi[2*]

Abstract

Background While home is frequently expressed as the favorite place of death (PoD) among terminally ill cancer patients, various factors affect the fulfillment of this wish. The determinants of the PoD of cancer patients in countries without healthcare system-integrated palliative and supportive care have not been studied before. This study aimed at identifying the predictors of the PoD of patients who suffer from advanced cancer by developing a reliable predictive model among who received home-based palliative care in Iran as a representative of the countries with isolated provision of palliative care services.

Methods In a cross-sectional study, electronic records of 4083 advanced cancer patients enrolled in the Iranian Cancer Control Center (MACSA) palliative homecare program, who died between February 2018 and February 2020 were retrieved. Multivariable binary logistic regression analysis as well as subgroup analyses (location, sex, marital status, and tumor topography) was performed to identify the predictors of PoD.

Results Of the 2398 cases included (mean age (SD) = 64.17 (14.45) year, 1269 (%52.9) male), 1216 (50.7%) patients died at home. Older age, presence and intensity of medical homecare in the last two weeks and registration in the Tehran site of the program were associated with dying at home ($P < 0.05$). Gynecological or hematological cancers, presence and intensity of the calls received from the remote palliative care unit in the last two weeks were predictors of death at the hospital ($p < 0.05$). The model was internally and externally validated (AUC = 0.723 (95% CI = 0.702–0.745; $P < 0.001$) and AUC = 0.697 (95% CI = 0.631–0.763; $P < 0.001$) respectively).

Conclusion Our model highlights the demographic, illness-related and environmental determinants of the PoD in communities with patchy provision of palliative care. It also urges policymakers and service providers to identify and take the local determinant of the place of death into account to match the goals of palliative and supportive services with the patient preferences.

Keywords End-of-life, Hospice, Terminal care, Malignant disease, Neoplasia, Oncology, Middle East

Support: This work was supported by the Iranian Cancer Control Center (MACSA) (M.S.Z.)

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Background

Cancer is the second cause of death and the foremost cause of morbidity worldwide [1] and palliative care is shown to alleviate the suffering of cancer patients and their families [2]. The first worldwide resolution on palliative care (World Health Assembly resolution WHA67.19) made in 2014, urged the World Health Organization (WHO) and its Member States to enhance the availability of palliative care [3]. Despite this, according to the "Global Atlas of Palliative Care" nearly half of the world's population lives in countries where palliative care is restricted to isolated providers that mainly govern on charitable donations (group 3a of WHO categorization of the palliative care development) [4]. Dying in the patient's preferred place is emerging as a consequential criterion of quality palliative care [5]. Various studies have indicated that patients who pass away in their homes, and their caregivers, experience a better quality of life than those who die in hospitals [6, 7]. Moreover, numerous studies have demonstrated that palliative care provided at home is linked to a reduced frequency of hospital admissions during the final months of life, fewer visits to the emergency room, and shorter hospital stays [8, 9].

Previous studies from countries with integrated palliative care suggest various factors may determine the place of death (PoD) of patients registered in palliative care programs [10]. A systematic review by Gomes and Higginson categorizes these factors into three groups: illness-related, individual and environmental factors. This study, performed in 2006, indicates that long length of disease, low physical performance, good social condition, the inclination for dying at home, availability and intensity of homecare services, rural environment, living with relatives, family support and being married are predictors of death at home [11], findings confirmed in more recent studies [12–15]. According to this study, non-solid malignancies, belonging to ethnic minorities, availability of inpatient beds and living in areas with a greater number of hospitals are associated with death at hospitals [11]. The study also reflects the effect of the geographical context of services on the determination of the PoD [11]. The intra- and inter-country variation of the predictors of the PoD show that the geographical context affects the predictors of the PoD [16–20]. While the past studies reflect the factors correlated with the PoD in countries where palliative care is integrated with mainstream health systems (group 4 of the WHO palliative care map) [21], to the best of our knowledge no research has determined the predictors of the PoD in other countries. Living in countries with minimally developed palliative care is associated with a poorer quality of death among cancer patients [22].

Iran is among the countries in group 3a of the WHO categorization of palliative care development [21] where palliative and supportive care is mainly provided by non-governmental providers [23]. Access to palliative care in Iran is limited to the services provided by the "Iranian Cancer Control Center" (aka MACSA, formerly "Ala Cancer Control Center"), the largest provider of palliative care services in Iran, and a few hospital-based palliative care programs [24]. However, a study performed in 2022 in Iran indicated that 75% of patients with advanced cancer preferred to stay at home at the end of their lives [25]. Iranian caregivers and nurses also agree that patients' death at home is preferred over other places [26]. Studies from other countries in group 3a including Egypt [27], South Africa [28], and India [29] also indicate that home is the preferred PoD for patients with advanced cancer.

This study aimed at identifying the predictors of the PoD of patients who suffer from advanced cancer in Iran, as an exemplar of the countries with patchy provision of palliative and supportive services. We developed and tested a clinical model for predicting the PoD of patients with advanced cancer who were registered in the home-based palliative care services in MACSA. We used the available basic demographic and clinical characteristics and routine healthcare data from the MACSA Distant services, including telephone counseling, are considered the components of the next generation of palliative care [30]. Thus, variables related to distant care, which are supposed to affect the PoD, were also included in the development of prediction models. Our study based on a large sample, as a first attempt provides new and comprehensive insights about the predictors of PoD of advanced cancer patients in a developing country different from rare studier done in these countries.

Methods

Design, setting, and population

We performed a retrospective database study with the data extracted from the MACSA Electronic Medical Records (EMR) system. MACSA is a charity organization pioneering non-governmental cancer palliative care in Iran. With nine sites in six cities of Iran, it offers a comprehensive package of outpatient, hospital, home-based, and remote palliative care services [24]. The homecare eligibility criterion for patients with histologically confirmed cancer in MACSA is the Palliative Performance Scale (PPS) ≤ 40 [24]. Medical homecare visits are performed by general practitioners (GPs) trained in palliative care, both periodically and based on patient demand. The remote telephone care is provided by trained palliative care GPs and includes periodic contact with patients and 24/7 telephone counseling. Ethical approval was obtained from the ethics committee of Isfahan University of Medical sciences (IR.MUI.MED.REC.1400.813). We only used the data from the patients or their legally authorized representatives who voluntarily provided written informed consent to use their routinely collected data for scientific purposes.

The patients who registered with any of the two major locations of MACSA in the Isfahan and Tehran homecare program and were deceased between February 20, 2018, and February 20, 2020, were included (*N*=4083). We selected this period to prevent the possible effects of the COVID-19 pandemic could have exerted on the determinants of the PoD [31]. The patients with less than two weeks of enrolment in palliative care services (*N*=683), aged below 18 years (*N*=7), or missing in any of the variables necessary for the development of the final model (*N*=995) were excluded. Figure 1 presents the flow diagram of the included and excluded cases from the analysis. Outlier values were removed based on the 1.5*IQR rule.

The prediction reported here conforms to the TRIPOD (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) checklist criteria [32].

Study variables

Independent variables were selected based on the previous literature and categorized based on Gomes and Higginson's systematic review categories [11]. Illness-related factors in our study include tumor topography, the number of comorbidities (0, 1, 2, ≥3), and smoking history. Demographic characteristics include age, gender, marital status (married, single, separated/divorced/widowed) and environmental factors include income quartile, residency status (native, immigrant/refugee), insurance, city of residence (Isfahan, Tehran), number of co-residing family members (CRFMs), mean age of the CRFM, mean of the age difference between patient and the CRFM, number of CRFM<18 years, days of enrolment in palliative service (DIP) and number of medical homecare visits (HC), number of periodic follow-up contacts from palliative care service to patient (CTP), number of calls from

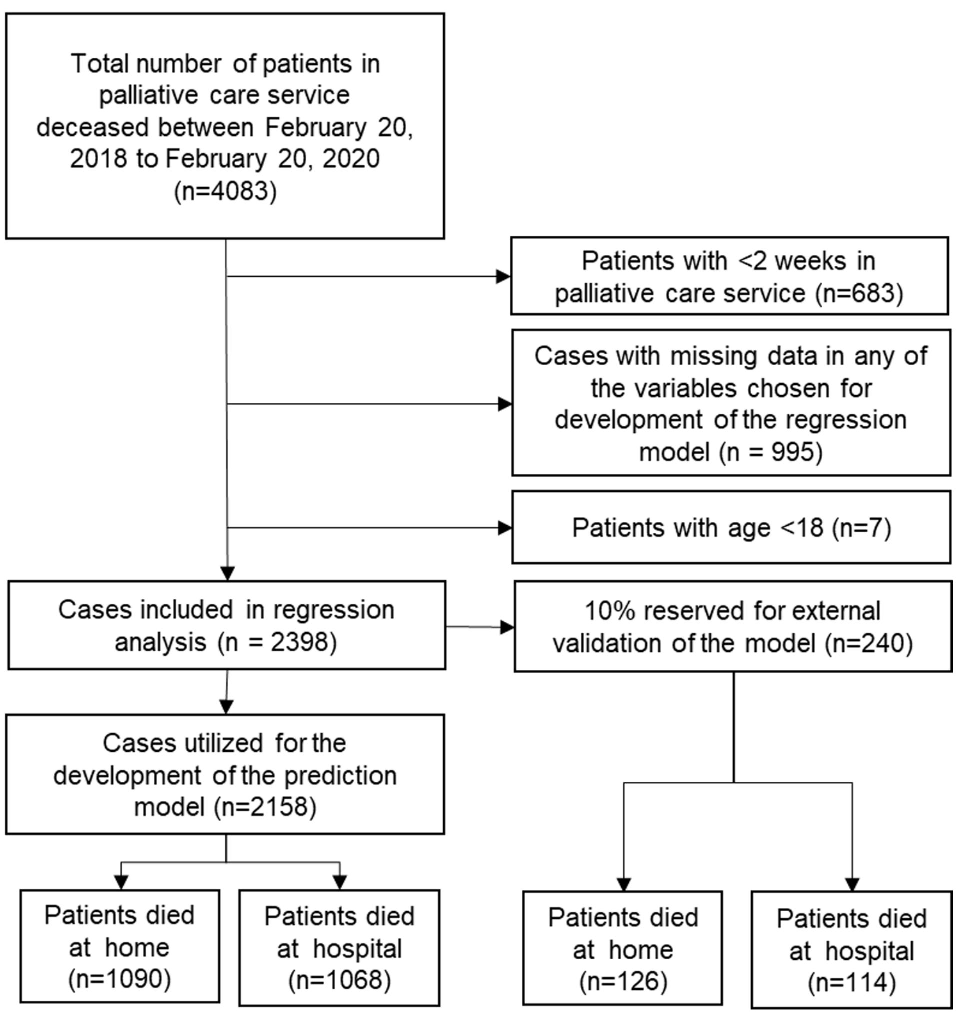

Fig. 1 Flow diagram of the data processing and analysis

patient or their caregiver to the palliative contact center (CFP) during the last two weeks of life, and the ratio of the duration of enrolment in palliative care service to the total period of diagnosis to death (DIP/T). The dependent variable, PoD, was determined according to the locally available places for care at the terminal phase of the disease in Iran (home and hospital).

Statistical analyses

The Kolmogorov-Smirnov test was utilized to assess the normality of the distribution of the continuous quantitative variables. Continuous normally and non-normally distributed variables were reported as mean ± standard deviation (SD) and median with interquartile range (IQR), respectively and categorical variables as frequency (percentage). Categorical and continuous variables were compared between categories of the PoD using Chi-Square (X^2), independent t-test and Mann-Whitney tests respectively.

To determine the predictive factors of PoD, multivariable binary logistic regression was utilized. Variables with overlapping concepts, less than 40 observations, and over 30% missing data were excluded to obtain higher precision in the estimation of the regression coefficients. Categorical variables were converted into dummy variables. The variables with a variance inflation factor (VIF) > 5 were identified as collinear and excluded. The variables with p-value < 0.1 in univariable analyses were included in the final multivariable analysis. We extracted and reserved 10% of the cases (N=240) randomly as the validation set, leaving 2158 cases for the development of the prediction model (Fig. 1). Discrimination of the models was measured via the area under the receiver operating characteristic (ROC) curve, AUC. External validation was performed by computing AUC for the main model in total sample and in the subgroup analysis.

We performed subgroup analyses to identify predictor variables associated with the outcome variable in different segments of the population. Separate logistic regression analyses were performed in the categories of sex, marital status, tumor topography and residency location. All statistical analyses were performed using IBM® SPSS version 26 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). P-value < 0.05 was considered as statistically significant level.

Table 1 Characteristics of the study population

Characteristic	Categories	Composition in total population
Gender, N (%)	Male	1269 (52.9%)
	Female	1129 (47.1%)
Age	Mean (SD)	64.17 ± 14.45
Place of death, N (%)	Home	1216 (50.7%)
	Hospital	1182 (49.3%)
Tumor topography, N (%)	Head and neck	289 (12.2%)
	Lung, bronchi, larynx	186 (7.8%)
	Breast	288 (12%)
	Digestive system	796 (33%)
	Kidney, urinary system, and prostate	243 (10.2%)
	Ovary and Uterus	139 (5.8%)
	Hematopoietic	145 (6%)
	Other	312 (13%)
Marital status, N (%)	Married	1811 (75.5%)
	Single	119 (5%)
	Separated/divorced/widowed	468 (19.5%)
Site, N (%)	Isfahan	1706 (71.1%)
	Tehran	692 (28.9%)

Results

Background characteristics

From the 2398 patients (mean age (SD) = 64.17 (14.45) year) included in the analyses, 1140 (52.8%) were male, 1536 (71.1%) were enrolled in Isfahan and 622 (28.9%) in Tehran site of the program, 1623 (79.8%) were married, 430 (19.9%) were separated, divorced or widowed and 105 (4.8%) were single (Table 1). The composition of our study sample roughly reflects the characteristics of the Iranian community of cancer patients [33]. An overall number of 1090 (50.5%) patients in the model development group and 126 (52.5%) patients in the validation group died at home (Fig. 1).

Univariate analysis results

The patient's mean age, mean age of co-residents, marital status, geographical location and the tumor topography were significantly different for patient died at home and hospital (p < 0.05). Patients who died at home had more medical visits, more CFP in the final two weeks of life and longer history of registration in palliative care services, while patients who died at the hospital had more CTP in the same interval to death (p < 0.001, Table 2).

Logistic regression analysis results

From the 25 considered predictors, variables 9 were selected for the development of the main regression model, based on the preceding criteria. Older age (OR: 0.97; 95%CI:0.97–0.98), presence of HC in the last two weeks of life (OR: 0.53; 95%CI:0.43–0.65), >1 HC in the last two weeks (OR: 0.12; 95%CI:0.09–0.17), and being enrolled in Tehran site of MACSA (OR: 0.49; 95%CI:0.39–0.61) were associated with dying at home (p < 0.05). Being diagnosed with gynecological (OR: 1.66; 95%CI:1.02–2.68) or hematological (OR: 1.66; 95%CI:1.04–2.64) cancers, presence of CTP in the last two weeks of life (OR:1.31; 95% CI:1.07–1.61) and >1 CTP in this period (OR: 1.62; 95%CI:1.24–2.12) were

Table 2 The bivariate analysis of the predictors of place of death

Categorical variables		Place of Death, N (%)		P value*
		Home (n = 1090)	Hospital (n = 1068)	
Gender	Male	554 (48.6%)	586 (51.4%)	0.06
	Female	536 (52.7%)	482 (47.3%)	
Site	Isfahan	712 (46.4%)	824 (53.6%)	< 0.0001
	Tehran	378 (60.8%)	244 (39.2%)	
Marital status	Married	792 (48.8%)	831 (51.2%)	0.006
	Single	51 (48.6%)	54 (51.4%)	
	Separated/divorced/widowed	247 (57.4%)	183 (42.6%)	
Tumor Topography	Head and neck	146 (55.9%)	115 (44.1%)	0.016
	Lung, bronchi, larynx	75 (44.6%)	93 (55.4%)	
	Breast	130 (49.1%)	135 (50.9%)	
	Digestive system	379 (53.4%)	331 (46.6%)	
	Kidney, urinary system and prostate	105 (49.1%)	109 (50.9%)	
	Ovary and uterus	56 (45.5%)	67 (54.5%)	
	Hematopoietic	49 (38.3%)	79 (61.7%)	
	Other	150 (51.9%)	139 (48.1%)	
Number of comorbidities	0	596 (49.9%)	598 (50.1%)	0.528
	1	257 (49.3%)	264 (50.7%)	
	2	156 (54%)	133 (46%)	
	≥ 3	81 (52.6%)	73 (47.4%)	
Income quartile	1st	77 (41%)	111 (59%)	0.185
	2nd	113 (44.8%)	139 (55.2%)	
	3rd	200 (45.5%)	240 (54.5%)	
	4th	90 (52.3%)	82 (47.7%)	
Residency status	Native	1069 (50.3%)	1055 (49.7%)	0.186
	Immigrant/refugee	21 (61.8%)	13 (38.2%)	
Insurance	No	12 (60%)	8 (40%)	0.393
	Yes	1076 (50.4%)	1059 (49.6%)	
Smoking	No	884 (50.6%)	863 (49.4%)	0.861
	Yes	206 (50.1%)	205 (49.9%)	
CRFM < 18 years?	No	485 (49.3%)	498 (50.7%)	0.022
	Yes	80 (40.4%)	118 (59.6%)	
HC in Last 6 months	0	12 (35.3%)	22 (64.7%)	< 0.0001
	1	177 (38.5%)	283 (61.5%)	
	2	209 (45.6%)	249 (54.4%)	
	3	190 (54.3%)	160 (45.7%)	
	≥ 4	502 (58.6%)	354 (41.4%)	
HC in Last 2 months	0	47 (35.6%)	85 (64.4%)	< 0.0001
	1	219 (38.3%)	353 (61.7%)	
	2	296 (45.7%)	352 (54.3%)	
	3	263 (59.8%)	177 (40.2%)	
	≥ 4	265 (72.4%)	101 (27.6%)	
HC in last 2 weeks	0	333 (36.2%)	588 (63.8%)	< 0.0001
	1	460 (52.9%)	410 (47.1%)	
	≥ 2	297 (80.9%)	70 (19.1%)	
CTP in last 6 months	0	140 (61.9%)	86 (38.1%)	< 0.0001
	1	302 (52.9%)	269 (47.1%)	
	2	206 (47%)	232 (53%)	
	3	171 (50.7%)	166 (49.3%)	
	≥ 4	271 (46.2%)	315 (53.8%)	

Table 2 (continued)

Categorical variables		**Place of Death, N (%)**				**P value***
		Home (n = 1090)		**Hospital (n = 1068)**		
CTP in last 2 months	0	241 (55.5%)		193 (44.5%)		< 0.001
	1	390 (52.3%)		355 (47.7%)		
	2	247 (51.1%)		236 (48.9%)		
	3	113 (44%)		144 (56%)		
	≥ 4	99 (41.4%)		140 (58.6%)		
CTP in last 2 weeks	0	578 (55.2%)		470 (44.8%)		< 0.0001
	1	357 (47.3%)		398 (52.7%)		
	≥ 2	155 (43.7%)		200 (56.3%)		
CFP in last 6 months	0	545 (48.8%)		572 (51.2%)		0.302
	1	123 (56.2%)		96 (43.8%)		
	2	85 (53.8%)		73 (46.2%)		
	3	66 (50%)		66 (50%)		
	≥ 4	271 (50.9%)		261 (49.1%)		
CFP in last 2 months	0	564 (48.4%)		601 (51.6%)		0.175
	1	134 (56.8%)		102 (43.2%)		
	2	91 (52.6%)		82 (47.4%)		
	3	72 (52.2%)		66 (47.8%)		
	≥ 4	229 (51.3%)		217 (48.7%)		
CFP in last 2 weeks	0	661 (47.8%)		721 (52.2%)		0.005
	1	166 (56.7%)		127 (43.3%)		
	2	100 (56.5%)		77 (43.5%)		
	3	52 (46%)		61 (54%)		
	≥ 4	111 (57.5%)		82 (42.5%)		
Continuous variables		Place of Death				P value
		Home (n = 1090)		Hospital (n = 1068)		
		Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Age (Years)		66.21 (13.75)	67 (58–77)	62.07 (14.86)	63 (53–73)	< 0.0001
Indicators of connection to palliative care	DIP	244.94 (407.05)	84.5 (38.25–241)	270.4 (411.37)	101 (43–301)	0.023
	DIP/T	0.39 (0.3)	0.32 (0.11–0.67)	0.4 (0.32)	0.33 (0.11–0.71)	0.334
CRFM characteristics	Number of CRFM	2.6 (1.6)	2 (1–3)	2.72 (1.55)	2 (2–4)	0.053
	Mean age of the CRFM	49.6 (17)	48 (37.55-62)	45.71 (16.3)	44.25 (34.68–56.87)	< 0.0001
	Average age difference between patients and CRFM	14.82 (13.67)	16.5 (5.25-24)	14.6 (13.55)	17 (6–24)	0.998

*Resulted from independent t-test or Mann-Whitney U test for continuous and chi-squared t-test for categorical variables. HC: homecare, CTP: call to patients; CFP: call from patients, DIP: days in palliative, DIP/T: days in palliative ratio to total days with disease, CRFM: Coresident family member

predictors of death at hospital. We evaluated the validity of fitted model internally by computing AUC. The AUC of the main model was 0.723 (95% CI = 0.702–0.745) (Fig. 2). The main model variables are presented in Table 3.

Subgroup analyses results

We conducted Subgroup analyses to identify predictors of PoD among various groups of patients. The adjusted odds ratios for these models are provided in supplementary Tables 1–4 (additional file 1). Our study indicated a significant difference between the two sites of the program in the prevalence of death at home. Subgroup analysis was performed to evaluate the impact of site-specific determinants on prediction performance (Fig. 3A and B). In Isfahan subgroup analyses, patients with Kidney, urinary system, or prostate cancer had a higher chance of dying at the hospital, though this was not the case for Tehran subgroup analyses ($p < 0.05$, Supplementary Table 1). The differential predictors of death at home were the number of CFP in the last two weeks of life for the Isfahan-specific model and being female for the Tehran-specific model (Supplementary Table 1). Other factors were the same for both subgroups. To further investigate the effect of other sociodemographic variables, subgroup analyses on sex (Fig. 3C and D, Supplementary Table 2) and marital status (Fig. 3E and G, Supplementary Table 3) were conducted. We conducted subgroup analyses stratified by tumor topography (Fig. 3H and O). Interestingly, the number of visits in the final two weeks of life

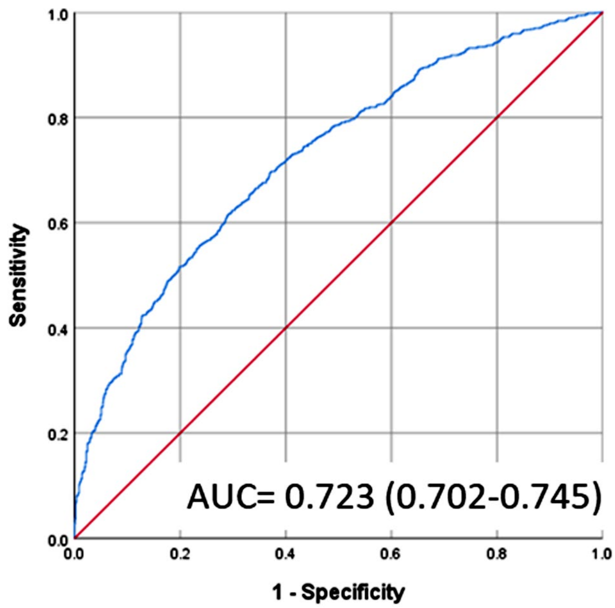

Fig. 2 Receiver operating characteristic curve of the internal validation of the main prediction model. The solid blue line indicates the relationship sensitivity versus specificity of the model. AUC, area under the curve

Table 3 The multivariable adjusted OR (95%CI) of the predictors of place of death

Predictors	Categories	OR (95% CI)	P value
Center	Isfahan	1	
	Tehran	0.494 (0.399, 0.611)	≤0.0001
Gender	Male	1	
	Female	0.822 (0.654,1.033)	0.093
Age		0.977 (0.97, 0.985)	≤0.0001
Marital status	Married	1	
	Single	0.643 (0.406, 1.019)	0.06
	Separated /divorced /widowed	0.917 (0.706, 1.191)	0.515
Tumor topography	Other	1	
	Head and neck	0.742 (0.515, 1.071)	0.112
	Lung, bronchi, larynx	1.42 (0.938, 2.15)	0.098
	Breast	1.28 (0.867, 1.89)	0.214
	Digestive system	1.083 (0.802, 1.463)	0.604
	Kidney, urinary system and prostate	1.254 (0.841, 1.869)	0.266
	Ovary and uterus	1.66 (1.026, 2.685)	0.039
	Hematopoietic	1.66 (1.043, 2.643)	0.033
Number of comorbidities	None	1	
	1	1.082 (0.861, 1.36)	0.499
	2	1.102 (0.824, 1.473)	0.514
	≥3	1.248 (0.855, 1.821)	0.251
DIP		1(0.99, 1.01)	0.574
HC in last 2 weeks	None	1	
	1	0.536 (0.438, 0.657)	<0.0001
	≥2	0.129 (0.096, 0.176)	<0.0001
CTP in last 2 weeks	None	1	
	1	1.315 (1.071, 1.616)	0.009
	≥2	1.625 (1.245, 2.12)	<0.0001
CFP in last 2 weeks	None	1	
	1	0.756 (0.571, 0.999)	<0.05
	2	0.781 (0.552, 1.105)	0.163
	3	1.247 (0.817, 1.903)	0.307
	≥4	0.79 (0.561, 1.114)	0.179

HC: homecare, CTP: call to patients; CFP: call from patients, DIP: days in palliative

was shown to be the most influential variable and was statistically significant in all topography-specific models developed (Supplementary Table 4). ROC curve analysis revealed AUCs are generally higher than the main model (Fig. 3). Interestingly in all subgroup models, the prediction ability of the number of physician home visits in the last two weeks had the highest impact on the PoD (Supplementary Tables 1–3).

External validation

The main prediction model and the models developed for subgroup analyses were tested on a validation set (N=240). The main model AUC was 0.697 (95% CI=0.631–0.763).

Discussion

We developed a model to predict the PoD of patients with advanced cancer receiving palliative homecare in Iran, as a representative of the countries with "isolated palliative care provision" (aka group 3a countries based on WHO categorization of the palliative care development [4]). We identified age, tumor topography, number of homecare visits in the last two weeks, number of CTPs in the last two weeks, and the site of registration as predictors of the PoD. In tumor-stratified subgroup analysis, models specific to hematopoietic and gynecologic cancers showed the highest accuracy and in site-specific subgroup analyses, the Tehran model had higher accuracy than Isfahan. The subgroup analyses for sex and marital status did not enhance the accuracy of prediction (Fig. 3C and G). We identified determinants of PoD among all three categories of variables suggested by Gomes and Higginson [11].

Similar to previous studies [34–36], our study identifies hematopoietic malignancies as a predictor of death at the hospital. Though previous studies attributed this to the fewer admissions of these patients to palliative care services [11], we identified hematopoietic cancers as a predictor of death at the hospital among the patients who were enrolled in a homecare palliative care program. Thus, we suggest that the higher likelihood of death at the hospital among these patients might be due to the different trajectories of hematopoietic malignancies [37]. The vicissitudinous nature of the hematological cancers is potentially associated with abrupt changes in patient's situation, emergency admissions to hospital and prolonged hospitalization and sometimes, unpredictable

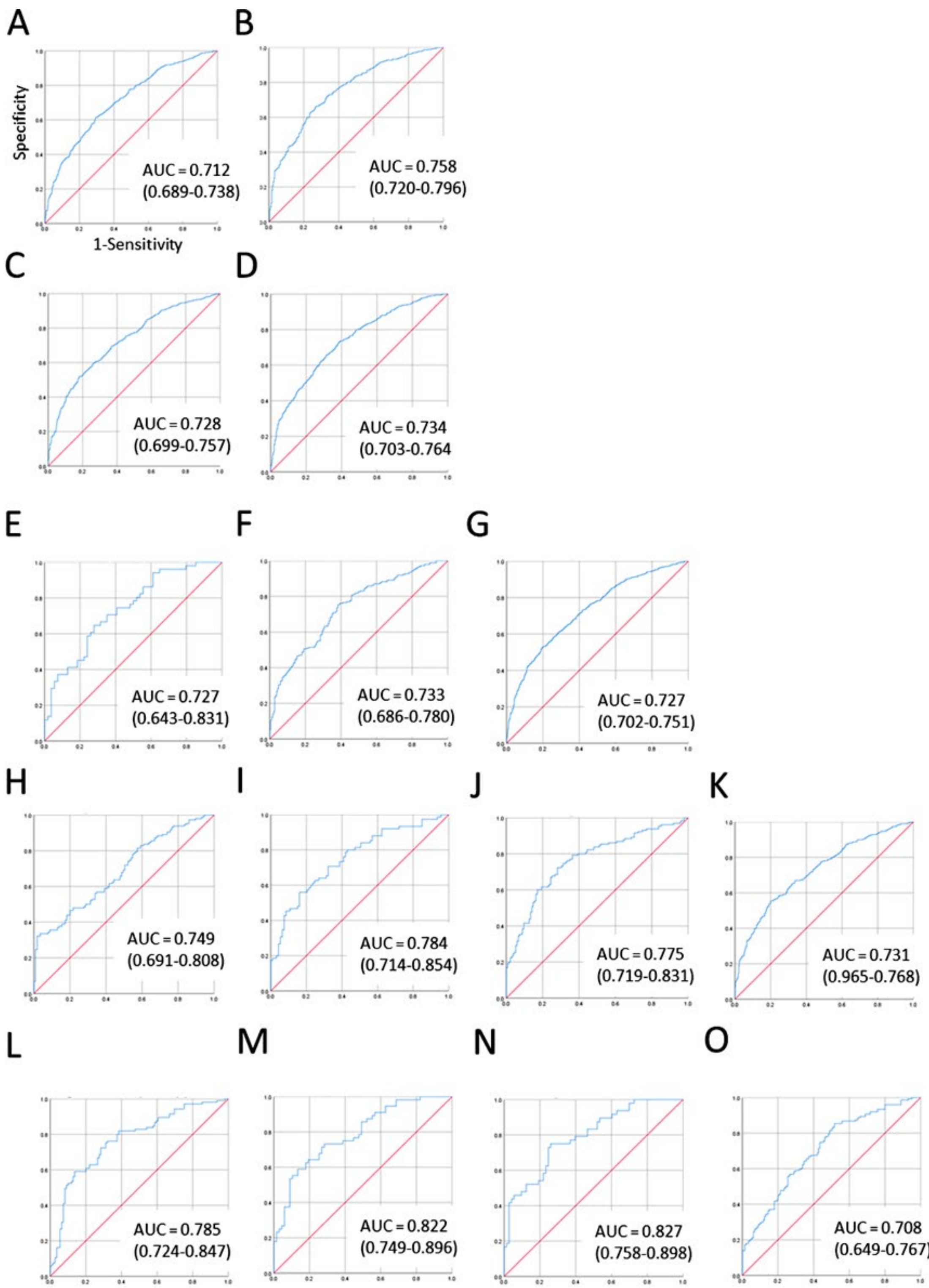

Fig. 3 Receiver operating characteristic curves of subgroup analyses. (**A**, **B**) location (**A**: Isfahan, **B**: Tehran), (**C**, **D**) sex (**C**: male, **D**: female), (**E**-**G**) marital status (**E**: single, **F**: widowed, divorced, separated, **G**: married), and (**H**-**O**) tumor topography (**H**: head and neck, **I**: respiratory system, **J**: breast, **K**: gastrointestinal tract, **L**: prostate, kidney and urinary system, **M**: gynecological system, **N**: hematopoietic, **O**: Other and cancers with unknown primary). AUC, area under the curve

death amid curative treatment period which collectively highlight the need for tailored end-of-life care for these patients. Likewise, our results show that gynecological cancers have a higher likelihood of death at the hospital. Although the incidence of gynecological cancers is limited to women, the observed difference may not be surrogated by sex differences since in our analyses, sex is not significantly associated with the PoD. A recent study by Kobo et al. that relies on data from circa 6 million American cancer patients points out that malignancy-related issues are the most common cause of hospital admissions among cancer patients [38], thus, future studies should consider the incorporation of cancer-related complications, that may differ by the types of malignancies, in prediction models of PoD.

While in our study the number of comorbidities was not associated with the PoD, Izquierdo-Porrera et al. identified the digestive comorbidities at the time of admission as a predictor of death at the hospital among men [39]. In addition, Kobo et al. identified infectious causes followed by gastrointestinal and cardiovascular causes as the most common non-malignancy-related causes of hospital admission among cancer patients [38]. Detailed coverage of chronic and acute health complications in medical records, utilizing standard recording systems like ICD-11 [40], and incorporating such data in future predictive models presumably fills this gap.

Among the individual factors we analyzed, the patient's gender and income quartile were not associated with the PoD and the higher age of the patient was a predictor of death at home. Gomes and Higginson highlighted 16 studies that inconsistently reported the predictive ability of age for PoD in their 2006 systematic review [11]. The predictive value of age has remained inconsistent in recent studies [13, 15]. We speculate that the significance of age as a predictor of PoD is linked to the local sociodemographic factors as well as available resources for elderly care, and thus may vary in different communities.

A recent study by Fereidouni et al. reported that over 75% of a group of Iranian advanced cancer patients preferred to die at home [25]. The concordance between the patient's preferred PoD and the actual PoD is an important indicator of the effectiveness of palliative care services [41], though, we did not include patients' preferences in our study. Identification of the patient's preferred PoD is hindered by the lack of legal and executive infrastructure of advanced directives in Iran and many other countries [42]. While this calls for the necessity of global implementation of advanced directives, on the other hand, a study from Korea indicated that nearly 70% of cancer patients who preferred to die at home have died in the hospital [14] suggesting that the identification of the preferred PoD cannot predict PoD per se.

In all models we generated, the prediction ability of the number of physician home visits in the last two weeks was statistically significant with the highest impact on the PoD. This can result from the potential ability of homecare visits to respond to the patient's needs at home in the final stage of life. This finding is in accord with the findings from earlier studies indicating that dying at home is correlated with ≥ 3 nurse home visits during the first week of homecare, ≥ 5 nursing home visits in the final week of life [16], the overall number of homecare visits [19] and overall number of physician visits [13]. Despite this, the total number of home visits, the number of visits by other medical professionals [13], the frequency of homecare visits in the final month of life [15] and the number of nurse visits [10, 13] have not contributed to the prediction of the PoD. The inconsistency between the specifications of services and the measures for intensity of care may have contributed to the different conclusions obtained in different studies. We also analyzed the effect of CTP and CFP on the PoD determination. While the number of CFPs was not associated with the PoD, unexpectedly the higher number of CTPs in the final two weeks of life was shown to be associated with an increased likelihood of death at the hospital.

We identified different powers of prediction of the main model in different sites of services. The site-specific subgroup models also differently weighted the predictors of death. This difference may reflect the variations in local practice, local standard of care, socio-geographical background, host community, and local access to other health care services. A study from Italy identified a significant variation in the proportion of deaths that occurred at home among 13 provinces where the study was performed, ranging from 31.4 to 73.3%. Differences in perception of dying at home among different cultural groups and inappropriate utilization of hospital services in different areas are suggested as the factors that underlie this finding [43]. Another study performed in Nova Scotia, Canada, indicates that patients residing in the metropolitan Halifax region were more likely to die at home than those living in other regions of the province. The article speculates that the difference in care culture and the public access to community-based services in different regions have led to this contrast [44]. Comparably, Temkin-Greener and Mukamel revealed that the prediction of the PoD varies across 12 different sites of the Program of All-Inclusive Care for the Elderly (PACE). The authors suggested the variation among PACE services and the local facilities as the reasons for the observed variation [18]. In this study, the distribution of demographic variables was not significantly different between the 2 sites of MACSA services (Supplementary Table 1). Thus, the difference in the proportion of home deaths in different sites rather seems to be - at least in part - a result of differences in sociological specifications and service-related variables (Supplementary Table 1). However, this is not limited to the variables explored in this study. These findings imply the importance of developing local models, incorporating social, cultural, logistic, and demographic specifications linked to each geographical location, especially for the countries in the preliminary stages of palliative care development.

Our study identified no correlation between income quartile, residency status, number of co-residing family members, presence of CRFM < 18 years, and the average age difference between patients and CRFM. Consonantly a study by Masucci et al. found that the caregiver's age or gender is not associated with the PoD [10]. However, the caregiver's age ≥ 55 years was shown to be connected with the patient's death at home in the model developed by Tay et al. [12]. The presence of caregivers [18] or co-residents [10] is shown to be a predictor of death at home in previous studies, a variable that is not measured in our study. Furthermore, marital status, which previously was shown to be a predictive factor of the PoD, did not emerge as a significant predictor of the PoD in this study.

Study limitations and strengths

To the best of our knowledge, this study is the first effort to develop a prediction model for PoD in countries with isolated provisions of palliative care, where the majority of annual human deaths occur [4]. This study is also the first of its kind in developing countries and also the west of Asia. This study benefits from a large sample size and the data collected during the early years of the development of a donation-based homecare cancer palliative service, which can give insight into the predictors of death in the early years of implementing palliative care in other similar countries. Another advantage of this work over past studies was the incorporation of the telemedicine-related variables, CTP and CFP to the prediction model.

Another point needs to be discussed is the possible effects of COVID-19 pandemic on changing patterns of death at home or hospital in cancer patients. Based on Turtle, L., et al., during the pandemic the cancer patients with COVID-19 have had a higher rate of death at hospital compared to the pre-pandemic era. Thus, it is tempting to speculate that the COVID-19 diagnosis could has served as a predictor for hospital death during the pandemic [45]. We could not find any article reporting changes in the health care system or cancer patients' needs in the post-pandemic era except that the incidence of some cancers has increased due to COVID-19 infection, however, it is unlikely that the care outcome and place of death has been affected by the changes in incidence since the overall change the incidence is not very large. To shed light on this question the same team is researching the changes in the incidence of symptoms experienced by cancer patients before, during COVID-19 and after COVID-19.

Our study was limited by the number of measured variables, especially social and psychological variables (including patient's and caregivers' preferred PoD, the cultural determinants of PoD, intimacy and emotional connection with the family and having independence in doing daily tasks at the end of life are among the psychological factors potentially affecting the preferred place of death), geographical variables (for example, patients' home distance from the health care centers) and patient's disease profile (type of comorbidities, symptoms and end of life complications). Overall, we considered many potential predictors of PoD, however as mentioned, we did not have access to some other important variables which led to diminishing the efficacy of our fitted prediction model reflected in its not so high sensitivity and specificity. Missing data in co-residency variables and income groups were other limitations. Our model does not distinguish hospital referrals at short intervals before death (e.g., < 24 h.) from longer periods of hospital admissions that concluded with death nor hospital referral by palliative care physicians. While this may challenge the number of visits in last two weeks of life as a predictive variable, this should be considered that our model identifies the effect of the intensity of service-related variables in last two weeks of life on PoD, regardless of the underlying mechanisms.

Some limitations arise from the fundamental complexity of research about death. While factors like cultural perspective on death and dying, the tendency to talk about death and communicating wishes, subcultures, and legal protocols can affect the patient's PoD, they are usually overlooked in studies that aim to develop a prediction model. The possible reason for such ignorance could be the complexity of measuring such variables. The other hurdle might be the difficulty of handling multiple questionnaires by patients, especially those in the final stages of their lives.

Conclusion

Further development of palliative care in countries with poor coverage of palliative care services, including those of the group 3a and integration of such services into the health system requires insight into the factors that potentially determine the demand for various services, including patient needs and the ability to predict the resources necessary for quality palliative care. As well such prediction models assist the policy makers to improve the infrastructure to fulfill the requirements of death at the patient's preferred place. This study highlights the necessity of local adjustment of the homecare services so that the local criteria for the satisfaction of patients and families are met. Our findings also foster the global utilization of medical informatics in palliative care to enhance the local collection, repositioning and analysis of data toward adjusting infrastructures and services to local needs. Further studies are suggested for developing more comprehensive predictive model of PoD by considering more relevant social, cultural and psychological background predictors.

Abbreviations

WHO	World Health Organization
PoD	Place of Death
AUC	Area Under the Curve
EMR	Electronic Medical Records
PPS	Palliative Performance Scale
GP	General Practitioners
COVID-19	Coronavirus disease 2019
IQR	Interquartile Range
TRIPOD	Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis
CRFMs	Co-Residing Family Members
HC	Home Care / Homecare
DIP	Days In Palliative
DIP/T	Days In Palliative to Total
SD	Standard Deviation
CTP	Calls To Patient
CFP	Calls From Patient
VIF	Variance Inflation Factor
ROC	Receiver Operating Characteristic
OR	Odds Ratio
CI	Confidence Interval
ICD-11	International Classification of Diseases 11th Revision
PACE	The Program of All-Inclusive Care for the Elderly
MD	Medical Doctor

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12904-024-01550-z.

Supplementary Material 1

Acknowledgements
The authors would like to thank the Iranian Cancer Control Center (MACSA) for their kind support. The authors also gratefully acknowledge support from Homayoun Naji Esfahani, director (Isfahan branch), Mohammad Reza Sharbafchi (MD), deputy director (technical), for providing clinical support, Dina Sadat Alavi (MD) for provision of her insightful clinical perspective and Hamzeh Ahmadi and Mostafa Ebadi for their methodological guidance in this research.

Author contributions
MSZ conceived the study concept and design. MSZ acquired and organized the data, conducted the analysis and wrote the first draft of the manuscript. AF supervised the analysis. Both authors contributed to the interpretation of the data. Both authors contributed to and approved the final manuscript.

Funding
This research was supported by Iranian Cancer Control Center (MACSA), Isfahan Branch (8184933473, Isfahan, Iran).

Data availability
Raw data used for this analysis are retrieved from MACSA EMR, which is not publicly available to preserve individuals' privacy under the Iranian National General Data Protection Regulation. Deidentified dataset is available from the corresponding author upon reasonable request. Other results of the analyses supporting the conclusions of this article are provided as supplementary data.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the ethics committee of Isfahan University of Medical sciences (IR.MUI.MED.REC.1400.813). We only used the data from the patients or their legally authorized representatives who voluntarily provided written informed consent to use their routinely collected data for scientific purposes at the time of filing at MACSA. The study conformed to the Declaration of Helsinki [46].

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 7 February 2024 / Accepted: 22 August 2024
Published online: 04 September 2024

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