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Prognosis Prediction Models and their Clinical Utility in Palliative Care

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Abstract

Prognosis prediction is a clinically relevant issue to facilitate optimal decision-making for both physicians and patients with cancer. Many previous studies revealed that prognosis prediction based on the physician's intuition and/or clinical experience is inaccurate and often optimistic, which means that there is a tendency to overestimate patient survival in daily clinical practice. In recent decades, many efforts have been made to develop prognosis prediction models which aid physicians to make more accurate prognosis prediction. In this chapter, we review the representative prognosis prediction models in palliative care and related studies. In addition, we refer to several prognosis prediction models developed by unique methods (for instance, case-crossover design or machine learning). Finally, we focus on the possible clinical utility of prognosis prediction models. In fact, no previous studies have clearly demonstrated whether the application of such prognosis prediction models truly benefits patient care in daily clinical practice. Therefore, we will discuss how the application of prognosis prediction models could benefit patients under palliative care.

Keywords: cancer, clinical prediction of survival, clinical utility, palliative care, prognosis prediction model

1. Introduction

Prognosis is one of the most relevant concerns for both patients and healthcare professionals (HCPs). Patients with advanced cancer and their families are required to make decisions such as choosing treatment alternatives or place to spend their end of life or that of their family members. In particular, timing in discontinuing palliative chemotherapy largely affects end-of-life care. Continuing ineffective palliative chemotherapy at the end of life increases life-threatening adverse events (AEs), hospital administration associated with AEs, and

medical cost [1, 2]. Furthermore, it causes patients' quality of life (QOL) to deteriorate, delays hospice referral, and deprives patients of the chance to die in their preferred place [3, 4]. Thus, optimal prognosis prediction is essential for better end-of-life care.

Subjective prognosis prediction based on HCPs' experience or intuition is a simple method, which requires no special device in daily practice. However, this method is often inaccurate or tends to overestimate patient survival [5]. Therefore, development of more accurate objective prognosis prediction methods is warranted.

In recent decades, several prognosis prediction models have been developed by integrating known prognostic factors [6–8]. These models have been validated in clinical settings across several countries and their accuracy have been compared [9, 10]. Moreover, studies exploiting new prognostic factors, such as phase angle or circadian rhythm, have been reported in Refs. [11, 12].

Recent progress in informatics has enabled us to retrieve and analyze clinical big data comprehensively, and new methods, such as machine learning or artificial intelligence, have been utilized to develop prognosis prediction models [13, 14]. We also review these issues in this chapter.

Finally, we focus on the clinical utility of prognosis prediction models, which has long been beyond the scope of the main issues in this research field.

2. Current status of prognosis prediction

2.1. Subjective prognosis prediction

Subjective prognosis prediction based on HCPs' experience or intuition is referred to as clinical prediction of survival (CPS). CPS is one of the most classic styles and has long been used in daily clinical practice. CPS utilizes three common questions. The first question is the "temporal" question, asking "how long can the patient live?" The second question is the "surprise" question, asking "will you be surprised if the patient dies within a specific term?" and the third question is the "probabilistic" question, asking "what is the patient's probability of survival within a specific term?"

The temporal question seems to be the most common prediction type in clinical practice. The answer to this question provides clear and simple information to HCPs. However, there are problems in its accuracy. Hui et al. reported its accuracy as just 32% among eight physicians and 18% among 20 nurses [15]. Moreover, 60% of nurses gave an optimistic prediction of survival [15]. Consistent with these results, another group reported that 63% of prognosis prediction estimated by HCPs was optimistic [16].

The surprise question has a feature of higher negative predictive value (NPV), which is more than 90% in two independent studies [17, 18]. Therefore, the surprise question has been used to identify patients who have a limited survival, and answering "no" is thought to signal the ideal time for specific action such as advance care planning (ACP) [19].

The probabilistic question showed a higher accuracy than the temporal question. The accuracy of physicians' prediction of death within 24 and 48 h was 71–73% and 66–67%, respectively [15, 20]. Interestingly, nurses showed more favorable predictive performance than physicians using the probabilistic question, and the accuracy of their prediction of death within 24 h and 48 h was 90–91% and 83–86%, respectively [15, 20].

2.2. Objective prognosis prediction

As discussed in Section 2.1, each CPS may have promising performance in specific settings; however, their accuracy is not satisfactory and is often optimistic [5, 16, 21]. To cope with these problems, many efforts have been made to develop more accurate prognosis prediction models using known prognostic factors.

2.2.1. Prognostic factors

Prognostic factors are classified into two groups, one composed of clinical signs/symptom and the other of laboratory data. Performance status [22–24], dyspnea [25, 26], malnutrition [27, 28], appetite/weight loss [29], and delirium [30, 31] are well-known clinical factors. Recently, novel prognostic factors have been proposed. Phase angle, which is measured via bioelectrical impedance analysis (BIA), reflects the amount of water in tissues (resistance) and cellular membrane (capacitance) and could be a prognostic factor [11]. Circadian rhythm is also found to be an independent prognostic factor [12, 32].

Laboratory factors include inflammatory markers (for instance, C-reactive protein (CRP), erythrocyte sedimentation, or neutrophil lymphocyte ratio) [33, 34], nutrition markers (for instance, albumin) [35, 36], and tumor progression markers (for instance, calcium or lactate dehydrogenase) [37, 38].

2.2.2. Prognosis prediction model

In recent decades, many prognostic models have been developed integrating a variety of prognostic factors, CPS, and other patients' information, and their accuracy is improving.

When we use these models in practice, we need to pay attention to the fitness of prediction models for treating patients. In other words, we should verify the clinical settings under which the prediction model was developed. When the clinical settings for treating patients are similar to those of the original study, the prognostic model may fit that patient; otherwise, we should exercise caution when applying prognostic models.

We reviewed the previously proposed prognostic models in the palliative care setting as shown below and summarized the characteristics of each model in **Table 1**.

2.2.2.1. The palliative prognostic index (PPI)

The palliative prognostic index (PPI) is a noninvasive prognostic model developed by Morita et al. in 1999 and requires no laboratory items (**Table 1**) [6].

Model	Items	Risk groups
Palliative prognostic index [6]	Palliative prognostic index (0–4 points) Oral intake (0–2.5 points) Edema (0, 1 point) Dyspnea at rest (0, 3.5 points) Delirium (0, 4 points)	(A) Median survival 155 days: PPI ≤ 2.0 (B) Median survival 89 days: 2.0 < PPI ≤ 4.0 (C) Median survival 18 days: 4.0 < PPI
Palliative prognostic score [7]	Dyspnea (0, 1 point) Anorexia (0, 1.5 points) Karnofsky performance scale ≥ 50% (0, 2.5 points) Clinical prediction of survival (0–8.5 points) Total white blood cell (0–1.5 points) Lymphocyte percentage (0–2.5 points)	(A) 30-Day survival probability > 70%, 0–5.5 points (B) 30-Day survival probability 30–70%, 5.6–11.0 points (C) 30-Day survival probability < 30%, 11.1–17.5 points
Glasgow prognostic score [62]	C-Reactive protein Albumin	Score 0: C-Reactive protein ≥ 10 mg/l and albumin ≥ 35g/l Score 1: C-reactive protein > 10 mg/l or albumin < 35 g/l Score 2: C-reactive protein >10 mg/l and albumin < 35 g/l
Prognosis in palliative care study predictor models A [8]	Mental test score >3 Pulse rate Presence of distant metastasis Site of metastases (liver) ECOG score Global health score Loss of appetite Site of metastases (bone) Difficulty in breathing Difficulty in swallowing Primary breast cancer Primary male genital cancer (including prostate) Weight loss	Days: <14 days Weeks: 14–55 days Months+: >55 days *See detail in “THE PiPS PROGNOSTICATOR”
Prognosis in palliative care study predictor models B [8]	Pulse rate White blood count Platelets Urea C-Reactive protein Global health score Alanine transaminase Mental test score >3 Distant metastasis Site of metastases (bone) Lack of appetite ECOG score Neutrophils Lymphocytes Alkaline phosphatase Albumin Primary male genital cancer (including prostate) Tired	Days: <14 days Weeks: 14–55 days Months+: >55 days *See detail in “THE PiPS PROGNOSTICATOR”

*THE PiPS PROGNOSTICATOR: <http://www.pips.sgul.ac.uk/>.

Table 1. Representative prognosis prediction models in palliative care.

Validation studies of the PPI were performed in Japan, Taiwan, Kuwait, Ireland, the United Kingdom, and Australia [39–46]. Morita et al. revealed that the PPI significantly reduced overestimation of survival compared to the CPS [39]. In the study of another group, the PPI was assessed by a nurse specialist, and the area under the curve (AUC) of the receiver operating characteristic (ROC) to predict death within 21 days was 0.68 [40]. In Kuwait, Alshemmari et al. revealed that the PPI can be a helpful tool in predicting hospital mortality of patients with advanced cancer in an acute care setting and that the hospital mortality rate for patients with a PPI score ≥ 6 was significantly higher than for those with a PPI score < 6 (93% versus 56% $p < 0.001$) [41].

In addition to the validation studies, studies which aimed to modify PPI were also reported. Two modified PPI models were tested in sub-analysis of the Japan-prognostic assessment tools validation (J-ProVal) study. The one substitutes the Communication Capacity Scale (CCS) for delirium to the required items of PPI [47]. The other adds a new item about the activities of daily living changes to the PPI; however, this did not significantly improve its prognostic value [48].

Moreover, some researchers examined the longitudinal score change of the PPI [49, 50].

2.2.2.2. Palliative prognostic (PaP) score

In 1999, Pirovano et al. proposed the palliative prognostic (PaP) score (**Table 1**) [7]. In this prospective cohort study, 519 patients with advanced cancer were recruited at 22 institutions in Italy, and a scoring model with a range of 0–17.5 points was developed. The score was able to subdivide the population into three risk groups [7]. The PaP score has been validated in both oncological and palliative settings.

In the palliative setting, the validation studies were performed in Australia, Italy, Brazil, and Canada [51–55]. Glare and Virik prospectively recruited 100 consecutive patients referred to palliative medicine consultative services. In this study, each of the three risk groups showed significantly different median survivals (60, 34, and 8 d, respectively) [51].

In the oncology setting, the validation studies were performed in Australia, Italy, and Japan [56–59]. Initially, a validation study of the oncology setting was reported by Glare et al. in 2004, recruiting 100 patients receiving medical or radiation oncology care [56]. The median survival of three risk groups was 17, 7, and < 1 w, respectively. A retrospective study of Ikeguchi et al. was unique because it revealed that patients with non-resectable gastric cancer who were classified into the low-risk group by the PaP score received a more toxic first-line regimen, whereas patients with a high-risk score received a less toxic regimen [57]. Ikeguchi et al. concluded that the PaP score may be a promising tool for selecting a chemotherapy regimen for patients with non-resectable gastric cancer.

Studies modifying the PaP score are also reported. In 2011, Scarpi et al. proposed the D-PaP score, which added the item of delirium into the PaP score [60]. Interestingly, Hui et al. revealed that the PaP score without the CPS showed a better predictive performance than the original PaP score in 2016 [61]. This suggested that the addition of the CPS to the PaP score may actually reduce its accuracy. Further comparison of the PaP score with or without the CPS would be of value.

2.2.2.3. Glasgow prognostic score (GPS)

The Glasgow prognostic score (GPS) is a simple prognostic model based on inflammatory markers, which requires only a CRP and albumin (**Table 1**). The GPS is a prognostic model with the most abundant evidence, and more than 60 papers recruiting more than 30,000 participants have been reported in Ref. [62].

However, studies of the GPS in a palliative care setting are scarce. Partridge et al. retrospectively examined the prognostic performance of 120 patients with advanced cancer at a single institution in the United Kingdom [63]. In this study, patients with a modified GPS of 2 had 2.7 times higher risk of death compared to those with a modified GPS of 0 [63]. In the J-ProVal study, Miura et al. prospectively recruited 1160 patients in palliative care settings [64]. They reported that the positive predictive value (PPV) and NPV of 6 weeks of prognosis of patients with a GPS of 2 were 0.733 and 0.611, respectively.

2.2.2.4. Prognosis in palliative care study (PiPS) predictor model

In 2011, Gwilliam et al. proposed the prognosis in palliative care study (PiPS) model (**Table 1**). In this prospective cohort study, 1018 patients with cancer were recruited from 18 institutions in the United Kingdom [8]. The PiPS-A model does not require laboratory items and showed an AUC of 0.79. The PiPS-B model requires laboratory items and showed an AUC of 0.86.

Since the PiPS model is a relatively newer prognostic model, the number of validation studies is limited [65, 66]. In 2015, Kim et al. reported a validation study of 202 patients with advanced cancer at the palliative care unit (PCU) in Korea [65]. Both the PiPS-A model and the PiPS-B model effectively predicted median survival in the “days” and “weeks” groups; however, it did not in the “months” group [65]. Further validation of the PiPS model is warranted.

2.2.3. Comparison among prognosis prediction models

Direct comparison of different prognostic models in the same cohort is important, because it indicates the usefulness and appropriate clinical use of each model. There are some comparative studies [9, 43, 67], and the largest is the J-ProVal study reported by Baba et al.

Baba et al. tested five different prognosis models: the PaP score, the D-PaP score, the PPI model, the PiPS-A model, and the PiPS-B model [10]. Concerning feasibility, prognostic models without laboratory tests (the PPI model and the PiPS-A model) showed more than 90% feasibility in all palliative care settings, including home care services. Meanwhile, the feasibility of the PaP score, the D-PaP score, and the PiPS-B model, all of which require laboratory items, was 60–80%. In particular, the feasibility of home palliative care services was only 30–40%. Concerning predictive value, the PPI showed a significantly lower C-index than the PaP score and the D-PaP score in almost all settings. The modified PiPS model showed equivalent or superior accuracy to the PaP score and the D-PaP score in all settings [10]. The authors concluded that the “PPI is simple and highly feasible, and seems to be suitable for routine clinical use for situations where rough estimates of prognosis are sufficient and/or patients do not want invasive procedures. Although the PiPS-A model requires 13 items, it provides higher predictive value without invasive procedure.

If laboratory items are available, the PaP score, D-PaP score and PiPS-B model would be more appropriate" [10].

2.2.4. Other prognosis prediction models

In addition to the abovementioned representative prognostic models, other prognostic models are proposed, including the indicator of poor prognosis [68], the Vitamin B12/CRP index [69, 70], the terminal cancer prognostic score [71], the Chuang prognostic score [72, 73], the prognostic 7-day survival formula [74], the Chinese prognostic scale [75], the computer-assisted model [76], the Japan palliative oncology study-prognostic index [77], the objective prognostic score [78, 79], the prognostic nomogram for terminally ill cancer patients [80], and the symptom-based predictive tool [81]. Further validation studies or comparative studies among those models are warranted.

2.2.5. Novel research fields of prognosis prediction models

2.2.5.1. Prediction of sudden unexpected death (SUD)

Prediction of sudden unexpected death (SUD) is a novel and pivotal research field. SUD has no clear definition, but it is often recognized as sudden death that occurs earlier than anticipated [82, 83]. Prevalence of SUD ranges between 0.5 and 23% in the palliative care setting [82]. SUD shows no impending death sign, such as nonreactive pupils, decreased urine output, and peripheral cyanosis, which makes SUD more difficult to predict [82]. Meanwhile, SUD exposes patients, caregivers, and HCPs to serious burden [84]. Particularly, SUD is significantly associated with depression, panic disorder, alcohol use disorder, or social isolation for caregivers or bereaved families [85, 86]. Thus, identifying factors relating to the occurrence of SUD is richly warranted.

2.2.6. Prognosis prediction model using machine learning techniques or artificial intelligence

Because of the progress in the field of informatics, big data can be managed more easily and promptly than ever before. Correspondingly, the number of publications applying novel informatics techniques is rising in clinical research. Prognosis prediction models using machine learning techniques or artificial intelligence have been proposed in the oncology setting [13, 14]. In the coming decades, multidisciplinary studies featuring collaborations between informatics specialists and HCPs are likely to be accelerated. In the palliative care setting, since invasive procedures are generally avoided, the amount of available clinical data—such as blood tests or imaging tests—is limited. This may cause delays in the progress of informatics in the palliative care setting. Therefore, improving data retrieving systems, including those subjective clinical symptoms recorded in text style (for instance, pain, nausea, and appetite loss), will play a key role in the progress of palliative care research.

3. Future plan

Many efforts, reviewed in this chapter, have been made toward developing prognostic models and improving their accuracy. We are also developing a novel prognosis prediction model,

which is “adaptable.” Conventional prognostic models are developed using the data obtained from a single time point (for instance, a baseline assessment date). This study design limits the use of these models under baseline conditions. Because patients’ condition during treatment course can change from the baseline, development of an adaptable prognosis prediction model, which could be applied at any time point after the initiation of chemotherapy, is warranted in practice. Thus, we are developing adaptable prognostic models for patients with cancer receiving chemotherapy [87]. In this case-crossover study, we recruited 2693 patients, and 3,471,521 laboratory data at 115,738 time points, representing 40 laboratory items that were monitored for 1 year before the death event, were applied in developing prognostic models. The prognosis prediction model utilizing albumin, lactate dehydrogenase, and neutrophils was selected based on its strong ability to predict death events within 1 month–6 months, and the AUC for 1-month and 2-month models was more than 0.80. We plan to compare this novel model with existing conventional models.

Meanwhile, apart from the effort to predict more accurate prognosis, we should also focus on the issue that no previous studies clearly demonstrated whether application of such prognosis prediction models truly benefits patient care in daily clinical practice. There are concerns that we may be satisfied merely with developing or using prognosis prediction models but pay less attention to assessing their clinical utility. Next, we consider how prognosis prediction can benefit patients.

3.1. Efficacy of prognosis prediction for cancer patients

3.1.1. Clinical utility of prognostic disclosure

First, how many patients are willing to have their prognosis disclosed to them? Although it differs across studies, the proportion is reported to be 40–60% [88, 89]. It was shown that patients were willing to know their life expectancy in greater detail than anticipated by HCPs [90]. Thus, HCPs need to disclose the prognosis properly to patients who want this information.

Studies investigating the clinical outcome of prognostic disclosure are scarce. To the best of our knowledge, there are no clinical trials, but a few observational studies have been reported. In 2015, Enzinger et al. reported on a large prospective cohort study, “Coping with Cancer” [91]. In this study, 590 patients with advanced cancer were analyzed, and patients for whom their prognosis was disclosed had a more realistic understanding of life expectancy than those for whom it was not (median patient self-estimates of life expectancy 12 months versus 48 months). Moreover, patients with a realistic understanding of life expectancy preferred comfort-oriented over life-prolonging care, with a higher likelihood of a do-not-resuscitate order without deteriorating the patients’ emotional well-being or the patient-physician relationship [91]. Despite the limitation of being an observational study, however, this study produced meaningful findings for the association between prognosis disclosure and advance care planning (ACP).

Many studies have investigated whether ACP benefited end-of-life management. In the “Coping with Cancer” study, Wright et al. showed that end-of-life discussion was significantly

associated with a less aggressive medical care (such as ventilation, ICU admission, and resuscitation), a reduction in the bereaved caregiver's grief or depression, and a longer hospice stay [92]. Other similar studies also showed consistent results [1, 93, 94].

3.1.2. *Clinical utility of prognosis prediction model*

The outcomes of prognosis disclosure based on prognostic models would be expected to be the same as the outcomes referred to in Section 3.1.1. Considering study design is a challenging issue. For example, prognosis disclosure based on prognostic models versus the CPS may be interesting, but it may also introduce some ethical issues that need to be resolved. We hope that the number of studies investigating the clinical utility of prognostic models will increase in the near future.

4. Conclusion

A number of prognosis prediction models are proposed, and their accuracy is approaching 80–90%. Novel techniques, such as machine learning or artificial intelligence, would accelerate progress. At the same time, we need to put greater efforts to clarify the clinical utility of prognosis prediction models for patients with cancer, a topic that has been beyond the scope of the main issues in this research field for a long time.

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