Clinical Signs of Impending Death in Cancer Patients

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Disclosures of potential conflicts of interest may be found at the end of this article.

ABSTRACT

Background. The physical signs of impending death have not been well characterized in cancer patients. A better understanding of these signs may improve the ability of clinicians to diagnose impending death. We examined the frequency and onset of 10 bedside physical signs and their diagnostic performance for impending death.

Methods. We systematically documented 10 physical signs every 12 hours from admission to death or discharge in 357 consecutive patients with advanced cancer admitted to two acute palliative care units. We examined the frequency and median onset of each sign from death backward and calculated their likelihood ratios (LRs) associated with death within 3 days.

Results. In total, 203 of 357 patients (52 of 151 in the U.S., 151 of 206 in Brazil) died. Decreased level of consciousness, Palliative Performance Scale ≤20%, and dysphagia of liquids appeared at high frequency and >3 days before death and had

low specificity (<90%) and positive LR (<5) for impending death. In contrast, apnea periods, Cheyne-Stokes breathing, death rattle, peripheral cyanosis, pulselessness of radial artery, respiration with mandibular movement, and decreased urine output occurred mostly in the last 3 days of life and at lower frequency. Five of these signs had high specificity (>95%) and positive LRs for death within 3 days, including pulselessness of radial artery (positive LR: 15.6; 95% confidence interval [CI]: 13.7–17.4), respiration with mandibular movement (positive LR: 10; 95% CI: 9.1–10.9), decreased urine output (positive LR: 15.2; 95% CI: 13.4–17.1), Cheyne-Stokes breathing (positive LR: 12.4; 95% CI: 10.8–13.9), and death rattle (positive LR: 9; 95% CI: 8.1–9.8).

Conclusion. We identified highly specific physical signs associated with death within 3 days among cancer patients. *The Oncologist* 2014;19:681–687

Implications for Practice: In this prospective observational study, we identified 5 physical signs (pulselessness of radial artery, respiration with mandibular movement, decreased urine output, Cheyne-Stokes breathing, and death rattle) that were associated with a high likelihood of death within 3 days. The presence of these tell-tale signs may assist clinicians to make the diagnosis of impending death, with implications for important decisions such as hospital discharges and enrollment onto a clinical care pathway at the end of life.

INTRODUCTION

Cancer is a leading cause of death worldwide [1]. Timely and accurate diagnosis of impending death (i.e., death within days) is of utmost importance to clinicians, patients, and families. Many important decisions related to the quality of end-of-life care, such as discharge planning, hospice transfers, and discontinuation of aggressive investigations and treatments are dependent on a patient's prognosis [2]. Currently, the utility of clinical care pathways at the end of life (e.g., the Liverpool care pathway) is limited by clinicians' inability to accurately diagnose impending death [3].

Clinicians often overestimate survival [4, 5] and hesitate to make the diagnosis of impending death without adequate supporting evidence.

The trajectory of cancer has been examined in patients with months and weeks of life expectancy [6–9]; however, the physical signs that occur in the last days and hours of life remain poorly understood [10]. The frequency and onset of many clinical signs associated with impending death have not been systematically examined. A better understanding of the frequency and onset of these signs and their diagnostic

Table 1. Definition of clinical signs

Physical sign	Description	Criteria for negative sign	Criteria for positive sign
Apnea periods	Prolonged pauses between each breath	None	<30 seconds; 30–60 seconds; >60 seconds
Cheyne-Stokes breathing	Alternating periods of apnea and hyperpnea with a crescendo-decrescendo pattern	Absent	Present
Death rattle	Gurgling sound produced on inspiration and/or expiration related to airway secretions	None	Audible if very close; audible at the end of bed; audible >6 meters from door of room
Dysphagia of liquids	Difficulty with fluid intake	Absent	Present
Decreased level of consciousness	Richmond Agitation Sedation Scale	−1 to 4	−2 to −5 (sedation)
Decreased performance status	Palliative performance scale, validated for assessing function (0%–100%)	30%–100%	≤20% (bed bound, completely dependent)
Peripheral cyanosis	Bluish discoloration of extremities	None	Toes; feet; up to knees
Pulselessness of radial artery	Inability to palpate radial pulse	Normal	Left; right; both
Respiration with mandibular movement	Depression of jaw with inspiration	Absent	Present
Urine output	Measured volume of urine over a 12-hour period	>3,600 mL; 2,401–3,600 mL; 1,201–2,400 mL; ≤101–1,200 mL	≤100 mL

performance may assist clinicians with the diagnosis of impending death. The primary objective of this prospective observational study was to determine the frequency and onset of 10 clinical signs associated with impending death (i.e., apnea periods, Cheyne-Stokes breathing, death rattle, dysphagia of liquids, decreased level of consciousness, Palliative Performance Scale (PPS) ≤20%, peripheral cyanosis, pulselessness of radial artery, respiration with mandibular movement, and urine output over the last 12 hours <100 mL) in cancer patients admitted to acute palliative care units (APCUs). Our secondary objective was to determine their diagnostic performance for impending death in 3 days.

METHODS

Study Setting and Criteria
The Investigating the Process of Dying Study is a prospective longitudinal observational study. We enrolled consecutive patients with a diagnosis of advanced cancer who were ≥18 years of age and admitted to the APCUs at MD Anderson Cancer Center (MDACC) in the U.S. between April 5, 2010, and July 6, 2010, and at Barretos Cancer Hospital (BCH) in Brazil between January 27, 2011, and July 1, 2011. The institutional review boards at both institutions approved this study and provided waiver of consent for patient participation. This approach was adopted to minimize distress during the consent process and to ensure that we could collect data on an inclusive sample. All clinicians who participated in this study signed the informed consent prior to patient enrollment.

Patients with advanced cancer and severe distress were admitted to APCUs for intensive symptom support and/or for facilitating transitions relating to goals of care (e.g., palliative), place of care (e.g., home), and teams of care (e.g., hospice). Both the 12-bed APCU at MDACC and the 45-bed APCU at BCH are situated within tertiary care cancer centers and provide comprehensive symptom management and psychosocial

support through an interdisciplinary team, active treatment of various complications, and discharge planning for acutely ill patients. Both APCUs have access to full arrays of diagnostic and therapeutic measures, such as computed tomography and intravenous antibiotics. The historical in-hospital mortality rate was 30% at MDACC and 70% at BCH [11].

Data Collection
To select clinical signs to be captured in this study, our research team conducted a literature review of published articles [10, 12–14] and educational materials [15] on the process of dying. We subsequently discussed these signs with participating palliative care physicians and nurses. The final list of 10 targeted bedside signs were selected based on their prevalence in the literature and included apnea periods, Cheyne-Stokes breathing, death rattle, dysphagia of liquids, decreased level of consciousness, decreased PPS, peripheral cyanosis, pulselessness of radial artery, respiration with mandibular movement, and decreased urine output.

Table 1 consists of a description of each sign and its coding. The level of consciousness was documented using the Richmond Agitation Sedation Scale (RASS), a validated 10-point numeric rating scale that ranges from −5 (unarousable) to +4 (very agitated), in which 0 denotes a calm and alert patient [16, 17]. For study purposes, a RASS score of −2 or lower was considered as decreased level of consciousness. The PPS is a validated 11-point scale ranging from 0% (death) to 100% (completely asymptomatic) based on the patient's function [18, 19]. A score of ≤20% indicates that the patient is completely bed bound and has limited survival [20].

We collected baseline patient demographics on admission. All nurses who participated in this study worked full time in palliative care and were experienced in providing care at the end of life. All nurses attended an orientation session to review the study objectives and data collection forms. Moreover, the principal investigators and charge nurses provided

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longitudinal support during the study by reviewing the forms on a daily basis to ensure they were complete and accurate and provided education to the nurses on an as needed basis. The two study sites had weekly video conferences to ensure data were collected systematically and accurately. The study forms were translated into Portuguese to facilitate data collection in Brazil and back-translated to ensure accuracy of translation. Every 12 hours from admission to discharge or death, clinical nurses completed standardized data collection forms independently of prior assessments. The 12-hour period was chosen based on the duration of the nursing shift.

Survival from time of APCU admission was collected from institutional databases and electronic health records.

Statistical Analysis

Our preplanned sample size was a combined total of 200 deaths in the two study sites. For signs with a prevalence of 10%, 30%, and 50%, the corresponding 95% confidence intervals (CIs) were 4.2%, 6.4%, and 6.9%, respectively. This sample size was able to provide a standard error of the Kaplan-Meier estimate at a particular time of ≤0.025 using the method described by Peto et al. [21, 22].

We summarized the baseline demographics using descriptive statistics. We documented the frequency of each sign and the median onset from death backward for all patients who died in the APCUs. The median time of death after first occurrence of each sign was estimated by the Kaplan-Meier method, conditional on observation of that particular sign or symptom. Patients were left censored if they entered the APCU with the sign already present.

To determine the diagnostic performance of each sign, we computed the sensitivity, specificity, positive likelihood ratio (LR), and negative LR using a 2 × 2 diagnostic table with random sampling, as described previously [23]. We used data from all 357 patients, instead of only those 203 patients who died, because it is the entire population in which the diagnostic test will be applied. We coded the diagnostic test result by dichotomizing all the signs into "absent" or "present" (Table 1). For each diagnostic test result, we then determined whether the patient died in the next 3 days. We selected 3 days as the cutoff for impending death because our data showed emergence of many of these signs during this period, and knowing a patient is in the last 3 days of life could have practical implications for integrated care pathways and discharge decisions. We subsequently constructed a 2 × 2 table with one observation per patient based on the presence or absence of change in a particular vital sign during a randomly sampled nursing shift and whether that patient died within the next 3 days. To account for the multiple observations for each patient, we resampled our data 100 times to obtain the average and 95% CI. Missing data were omitted from the analyses.

Positive LR provides an estimate of how many times more or less likely patients who died within a given time period are to have a particular physical sign than patients who did not die, and it is commonly used in diagnostic studies [24]. Positive LRs of >5 and >10 correspond to good and excellent discriminatory test performance, respectively [24].

SAS version 9.2 (SAS Institute, Cary, NC, http://www.sas.com) was used for statistical analysis. Urinary output was not routinely collected at BCH.

RESULTS

Patient Characteristics

Consistent with our projection, 52 of 151 MDACC patients (34%) and 151 of 206 BCH patients (73%) died in the APCU. Table 2 shows the patient characteristics at APCU admission. At the time of analysis, 46 (13%) remained alive, with a median follow-up of 61 days.

Frequency and Onset of Clinical Signs

Table 3 shows the frequency of each clinical sign among the patients who died in the APCU. Three signs (PPS ≤20%, RASS −2 or lower, and dysphagia of liquids) were documented in a substantial proportion of patients over the last 7 days of life, occurring in a majority of decedents 12 hours before death.

In contrast, seven other signs (apnea periods, Cheyne-Stokes breathing, death rattle, peripheral cyanosis, pulselessness of radial artery, respiration with mandibular movement, and decreased urine output) were documented in fewer than half of the patients, even in the last 12 hours of life.

The onset of the 10 clinical signs is shown in Figure 1A. The median onset was 4 days, 4.5 days, and 7 days prior to death for PPS ≤20%, RASS −2 or lower, and dysphagia of liquids, respectively. In contrast, the seven other signs had a median onset of 3 days or less before death. The average number of these seven signs increased in the last 3 days of life (Fig. 1B).

Diagnostic Performance of Clinical Signs

Table 4 illustrates the diagnostic performance of the 10 clinical signs. The seven signs that emerged in the last 3 days of life had high specificity (>95%), low sensitivity (<60%), and high positive LR for impending death in 3 days. Specifically, the positive LRs were 15.6 (95% CI: 13.7–17.4) for pulselessness of radial artery, 15.2 (95% CI: 13.4–17.1) for decreased urine output, 12.4 (95% CI: 10.8–13.9) for Cheyne-Stokes breathing, 10 (95% CI: 9.1–10.9) for respiration with mandibular movement, and 9 (95% CI: 8.1–9.8) for death rattle. In contrast, PPS ≤20%, RASS −2 or lower, and dysphagia of liquids had higher sensitivity, lower specificity, and lower positive LR.

DISCUSSION

Despite the universality and fundamental nature of the dying process, little is known about the frequency and onset of clinical signs that occur in the last days of life [12, 14, 25, 26]. By systematically examining the frequency and onset of 10 clinical signs, we were able to divide them into two categories: early and late signs. Early signs were observed relatively frequently and include decreased performance status, decreased oral intake, and decreased level of consciousness. Because of their low specificity, these signs could not reliably predict impending death in 3 days. In contrast, late signs emerged only in the last few days of life in a smaller proportion of patients and had high positive LR for impending death in 3 days. The use of late physical signs may assist clinicians in making the diagnosis of impending death.

Impending death is a diagnostic issue rather than a prognostic phenomenon because these signs indicate the presence of an irreversible physiologic process, similar to the diagnosis

Table 2. Patient characteristics

Characteristics	All patients (n = 357)[a]	Patients who were alive at APCU discharge (n = 154)[a]	Patients who died in APCU (n = 203)[a]	p value
Age, average (range)	58 (18–88)	57 (18–86)	58 (18–88)	.21[b]
Female sex, n (%)	195 (55)	96 (62)	99 (49)	.01[c]
Ethnicity, n (%)				<.001[d]
White	98 (28)	60 (39)	38 (19)	
Black	21 (6)	15 (10)	6 (3)	
Hispanic	233 (65)	75 (49)	158 (78)	
Others	5 (1)	4 (3)	1 (1)	
Christian religion, n (%)	329 (93)	136 (89)	193 (96)	.02[c]
Married, n (%)	206 (58)	92 (61)	114 (57)	.47[c]
Education, n (%)				.12[c]
High school or lower	243 (76)	96 (71)	147 (80)	
College	59 (18)	32 (24)	27 (15)	
Advanced	17 (5)	7 (5)	10 (5)	
Cancer, n (%)				.13[c]
Breast	40 (11)	20 (13)	20 (10)	
Gastrointestinal	101 (28)	33 (21)	68 (33)	
Genitourinary	37 (10)	16 (10)	21 (10)	
Gynecological	41 (11)	25 (16)	16 (8)	
Head and neck	26 (7)	10 (6)	16 (8)	
Hematological	17 (5)	7 (5)	10 (5)	
Others	44 (12)	21 (14)	23 (11)	
Respiratory	51 (14)	22 (14)	29 (14)	
Comorbidities, n (%)				
Chronic obstructive pulmonary disease	16 (4)	12 (8)	4 (2)	.01[d]
Heart failure	17 (5)	8 (5)	9 (4)	.74[c]
Coronary artery disease	13 (4)	9 (6)	4 (2)	.08[d]
Stroke	8 (2)	4 (3)	4 (2)	.73[d]
Chronic kidney disease	5 (1)	4 (3)	1 (0.5)	.09[d]
Diabetes	50 (14)	22 (14)	28 (14)	.89[d]
Months between cancer diagnosis and palliative care unit admission, median (IQR)	15 (6–34)	20 (9–46)	13 (4–31)	.002[e]
Duration of palliative care unit admission, days, median (IQR)	6 (4–9)	7 (5–9)	5 (2–9)	<.001[e]

[a]Unless otherwise specified.
[b]t test.
[c]χ^2 test.
[d]Fisher exact test (expected cell count <5).
[e]Mann-Whitney test.
Abbreviations: APCU, acute palliative care unit; IQR, interquartile range.

of a pregnancy or labor. The ability to make this diagnosis confidently is of great significance because many critical decisions such as enrollment into integrated care pathways and discharge planning are based on this diagnosis. Although some of the signs identified in this paper have been described anecdotally in review articles and books [10, 12–14], this is the first study to systematically characterize their frequencies, onset, and LRs, allowing clinicians to differentiate their relative importance and utility for the diagnosis of impending death. Our findings suggest that simple bedside physical findings may help clinicians make the diagnosis of impending death.

Our findings also explain why it is difficult for clinicians to diagnose impending death in advance. Although the presence of late signs strongly suggest that death is imminent, these signs are observed relatively infrequently and only in the last few days of life. Importantly, their absence could not rule out the possibility that the patient will die shortly, because their sensitivity is low. In contrast, early signs are common, are present early, and have only moderate positive LRs (<5) for impending death in 3 days.

Kehl et al. conducted a systematic review of the signs and symptoms and identified very few studies on the signs of

Table 3. Frequency of 10 clinical signs before death

Physical signs	Frequency of each sign before death, n/N (%)[a]															Frequency of sign in last 3 days of life, n (%)[b]
	−7.0 days	−6.5 days	−6.0 days	−5.5 days	−5.0 days	−4.5 days	−4.0 days	−3.5 days	−3.0 days	−2.5 days	−2.0 days	−1.5 days	−1.0 days	−0.5 days	
PPS ≤20%	23/65 (35)	24/70 (34)	26/75 (35)	28/81 (35)	29/90 (32)	36/98 (36)	47/110 (43)	50/124 (40)	64/133 (48)	76/147 (52)	93/164 (56)	105/179 (59)	143/195 (73)	166/203 (82)	169 (93)
RASS −2 or lower	14/65 (22)	12/70 (17)	19/75 (26)	22/81 (27)	30/90 (34)	31/98 (32)	47/110 (43)	41/124 (33)	59/133 (44)	62/147 (42)	79/164 (48)	91/179 (51)	121/195 (62)	151/203 (74)	159 (90)
Dysphagia of liquids	20/61 (33)	23/66 (35)	26/69 (38)	25/70 (36)	28/77 (36)	29/87 (33)	37/91 (41)	39/103 (38)	37/104 (36)	47/115 (41)	53/125 (42)	49/121 (40)	50/108 (46)	41/76 (54)	100 (90)
Urine output over last 12 hours <100 mL	1/20 (5)	0/23 (0)	3/25 (12)	0/25 (0)	1/34 (3)	1/36 (3)	3/37 (8)	3/51 (6)	7/55 (13)	6/61 (10)	6/68 (9)	13/72 (18)	23/80 (29)	30/75 (40)	48 (72)
Death rattle	3/65 (5)	2/68 (3)	3/74 (4)	7/78 (9)	4/89 (4)	8/97 (8)	10/110 (9)	18/123 (15)	15/133 (11)	14/144 (10)	29/163 (18)	35/176 (20)	56/195 (29)	78/202 (39)	110 (66)
Apnea periods	2/65 (3)	4/69 (6)	3/74 (4)	5/78 (6)	6/89 (7)	5/97 (5)	6/109 (6)	7/123 (6)	13/133 (10)	12/145 (8)	18/164 (11)	30/177 (17)	37/194 (19)	66/201 (33)	71 (46)
Respiration with mandibular movement	1/64 (2)	2/69 (3)	3/74 (4)	1/78 (1)	3/89 (3)	4/97 (4)	6/110 (5)	9/123 (7)	15/133 (11)	10/145 (7)	20/163 (12)	29/177 (16)	50/195 (26)	65/202 (32)	92 (56)
Peripheral cyanosis	7/65 (11)	4/69 (6)	9/74 (12)	8/78 (10)	7/89 (8)	11/97 (11)	17/109 (16)	13/123 (11)	19/133 (14)	26/145 (18)	30/164 (18)	35/177 (20)	49/195 (25)	80/201 (40)	99 (59)
Cheyne-Stokes breathing	3/65 (5)	3/69 (4)	1/74 (1)	0/78 (0)	2/89 (2)	4/97 (4)	3/110 (3)	5/123 (4)	7/133 (5)	7/145 (5)	14/164 (9)	20/177 (11)	23/194 (12)	46/202 (23)	61 (41)
Pulselessness of radial artery	1/65 (2)	1/69 (1)	0/74 (0)	0/78 (0)	0/89 (0)	2/97 (2)	1/108 (1)	5/123 (4)	4/132 (3)	5/144 (3)	6/163 (4)	8/176 (5)	18/194 (9)	48/200 (24)	57 (38)

[a]The nominator was the number of patients with a sign of interest, the denominator was the number of patients with data at the particular time point. The number of patients in the denominator varied because of the different duration of hospitalization among patients and missing data. For instance, urinary output was not routinely collected at Barretos Cancer Hospital.

[b]Any occurrence of the sign of interest within the last 3 days of life among patients who died in the acute palliative care unit.

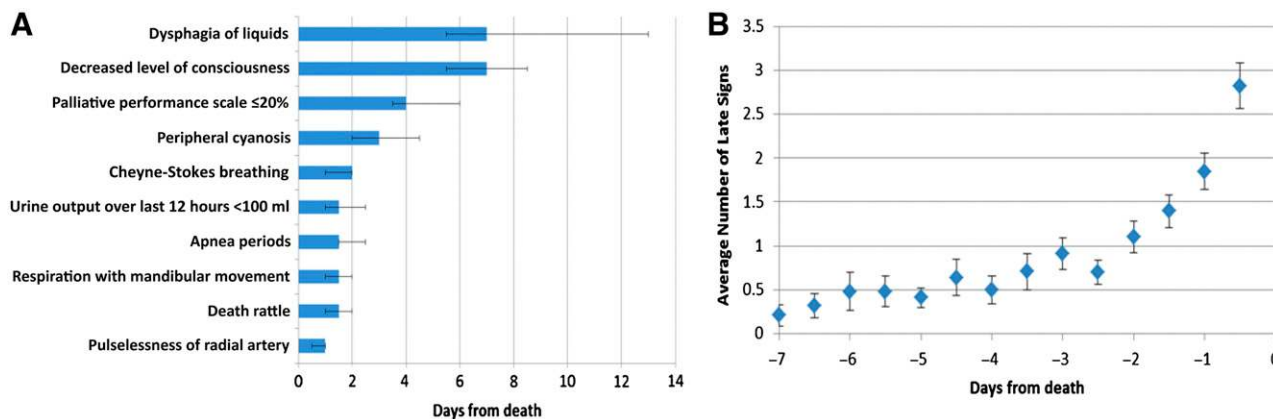Abbreviations: PPS, Palliative Performance Scale; RASS, Richmond Agitation Sedation Scale.

Figure 1. Frequency and onset of clinical signs among 203 patients who died in acute palliative care units. **(A):** The median time of onset (95% confidence interval) is shown. The median onset was ≤3 days before death for seven of these signs. **(B):** The average number of the seven late signs (apnea periods, Cheyne-Stokes breathing, death rattle, peripheral cyanosis, pulselessness of radial artery, respiration with mandibular movement, and decreased urine output) are shown over time, with error bars indicating standard errors.

impending death [27]. The OPCARE9 project recently used a Delphi survey by international experts to identify key clinical signs associated with impending death [28]. They recommended 10 phenomena for further examination (e.g., degradation of general condition, no fluid or food intake, conscious level changes, death rattle, breathing pattern changes) that were similar to our list of 10 signs chosen for this study.

Early signs are useful because they inform us that the patient is deteriorating. Based on the literature, the presence of these signs indicates a survival of weeks or less [11, 20, 29].

Seow et al. showed that PPS declined sharply 4–6 weeks before death in a cohort of cancer patients [6]. Our data added to this by demonstrating that both performance status and level of consciousness continue to deteriorate rapidly in the last week of life. A majority of patients present with these early signs in the last days of life. Because of their lower specificity, early signs cannot reliably inform us that death is imminent.

Late signs are important because their appearance suggests that the patient likely has survival only in terms of days or less. Interestingly, these signs occurred only in the last days

Table 4. Diagnostic performance of 10 target clinical signs ($n = 357$)

Physical signs	Missing data, n (%)[a]	Sensitivity[b] (95% CI)	Specificity[b] (95% CI)	Negative LR[b] (95% CI)	Positive LR[b] (95% CI)
PPS ≤20%	120 (2.1)	64 (63.4–64.7)	81.3 (80.9–81.7)	0.44 (0.43–0.45)	3.5 (3.4–3.6)
RASS −2 or lower	90 (1.6)	50.5 (49.9–51.1)	89.3 (88.9–89.7)	0.6 (0.5–0.6)	4.9 (4.7–5)
Dysphagia of liquids	652 (11.7)	40.9 (40.1–41.7)	78.8 (78.3–79.2)	0.75 (0.74–0.76)	1.9 (1.9–2)
Urine output over last 12 hours <100 mL	3262 (58)	24.2 (23.2–25.1)	98.2 (98–98.5)	0.77 (0.76–0.78)	15.2 (13.4–17.1)
Death rattle	101 (1.8)	22.4 (21.8–22.9)	97.1 (96.9–97.3)	0.8 (0.79–0.81)	9 (8.1–9.8)
Apnea periods	85 (1.5)	17.6 (17.1–18)	95.3 (95.1–95.6)	0.86 (0.86–0.87)	4.5 (3.7–5.2)
Respiration with mandibular movement	86 (1.5)	22 (21.5–22.4)	97.5 (97.3–97.6)	0.8 (0.8–0.81)	10 (9.1–10.9)
Peripheral cyanosis	90 (1.6)	26.7 (26.1–27.3)	94.9 (94.7–95.2)	0.77 (0.77–0.78)	5.7 (5.4–6.1)
Cheyne-Stokes breathing	83 (1.5)	14.1 (13.6–14.5)	98.5 (98.4–98.7)	0.9 (0.9–0.9)	12.4 (10.8–13.9)
Pulselessness of radial artery	94 (1.7)	11.3 (10.9–11.8)	99.3 (99.2–99.5)	0.89 (0.89–0.9)	15.6 (13.7–17.4)

[a]Urinary output was not routinely collected at Barretos Cancer Hospital.
[b]We computed the sensitivity, specificity, positive LR, and negative LR for each sign for death within 3 days using data from all 357 patients. We constructed a 2 × 2 table with one observation per patient based on the presence or absence of a particular sign during a randomly sampled nursing shift and whether that patient died within the next 3 days from that shift, and then we calculated the sensitivity, specificity, positive LR, and negative LR. To account for the multiple observations for each patient, we resampled our data 100 times to obtain the average and 95% confidence interval for each statistic.
Abbreviations: CI, confidence interval; LR, likelihood ratio; PPS, Palliative Performance Scale; RASS, Richmond Agitation Sedation Scale.

of life and at relatively low frequencies; for instance, only 54% of patients had any of these seven signs in the last 12 hours before death. The frequency of death rattle in our study (66%) is consistent with others [14, 30–32]. Consequently, their absence cannot rule out imminent death, but their presence can be highly informative. The positive LRs for pulselessness of radial artery, decreased urine output, Cheyne-Stokes breathing, respiration with mandibular movement, and death rattle were particularly high. Based on the pretest probability and positive LR, the post-test probability for impending death can be determined using either a nomogram or a formula: $Prob^{post} = (Prob^{pre} / [1 - Prob^{pre}] \times LR+) / (1 + [Prob^{pre} / (1 - Prob^{pre}) \times LR+])$. For example, the pretest probability of dying within 3 days after admission to our APCUs was 38%. The presence of respiration with mandibular movement (positive LR: 10) in a patient results in a post-test probability of 86% ([0.38 / (1 − 0.38) × 10] / [1 + (0.38 / (1 − 0.38) × 10)]). Upon external validation in larger samples, the use of these signs alone or in combination could facilitate the diagnosis of impending death.

This study was powered based on the combined data. Notably, the two APCUs had different mortality rates because of different referral patterns and patient characteristics. When analysis was conducted by site, we found comparable specificities and sensitivities for the signs between the two participating institutions, and this finding further strengthens our results. Furthermore, because LRs are less dependent on prevalence, they are particularly suited for this analysis.

This study has several limitations. First, we included only cancer patients who were admitted to APCUs in the Americas, where they received intensive symptom management and interprofessional support [33]. Further studies are needed to determine whether the process of dying is similar in other settings and in noncancer illnesses. Second, we may have underestimated the frequency of some signs because of active interventions in the APCUs (e.g., death rattle); however, it would have been unethical to withhold treatments. Third, variations in the prevalence of some signs may be related to

patient differences, cancer diagnoses, and/or how they were interpreted. The data were highly compatible when analyzed by study site, demonstrating similar specificities and sensitivities for each sign. Fourth, we relied on highly trained nurses instead of physicians to document the clinical signs because they spend more time at patients' bedsides. All nurses received an orientation before study initiation and support throughout the study. Fifth, we did not assess the inter-rater reliability of these signs. Further validation is needed. Sixth, this study focused only on 10 physical signs; the frequency and diagnostic performance for other bedside signs would need to be examined. Finally, this study included only two centers with relatively small patient populations, and the signs were collected every 12 hours, which limited the resolution of data. Future studies should examine the cardinal signs in greater detail.

CONCLUSION

We methodically documented the frequency, onset, and diagnostic performance of 10 signs in cancer patients admitted to APCUs. On further validation, the late signs may assist clinicians in formulating the diagnosis of impending death, help patients and families in preparing ahead, and support researchers in further investigating the process of dying.

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