

A Review of Clinical Signs and Symptoms of Imminent End-of-Life in Individuals With Advanced Illness

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Abstract

Background: World population is not only aging but suffering from serious chronic illnesses, requiring an increasing need for end-of-life care. However, studies show that many healthcare providers involved in the care of dying patients sometimes express challenges in knowing when to stop non-beneficial investigations and futile treatments that tend to prolong undue suffering for the dying person. **Objective:** To evaluate the clinical signs and symptoms that show end-of-life is imminent in individuals with advanced illness. **Design:** Narrative review. **Methods:** Computerized databases, including PubMed, Embase, Medline, CINAHL, PsycInfo, and Google Scholar were searched from 1992 to 2022 for relevant original papers written in or translated into English language that investigated clinical signs and symptoms of imminent death in individuals with advanced illness. **Results:** 185 articles identified were carefully reviewed and only those that met the inclusion criteria were included for review. **Conclusion:** While it is often difficult to predict the timing of death, the ability of healthcare providers to recognize the clinical signs and symptoms of imminent death in terminally-ill individuals may lead to earlier anticipation of care needs and better planning to provide care that is tailored to individual's needs, and ultimately results in better end-of-life care, as well as a better bereavement adjustment experience for the families.

Keywords

end-of-life, chronic diseases, functional assessment, palliative care, hospice

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Introduction

Globally, by 2060, approximately 48 million people (47% of all deaths) will die from serious life-threatening illnesses, which amounts to a staggering 87% increase from 26 million people who died in 2016 (Sleeman et al., 2019). The world population is not only aging but suffering from many advanced, incurable, and progressive chronic illnesses, requiring an increasing need for end-of-life (EOL) care (Cruz-Oliver, 2017). Worldwide Palliative Care Alliance reports that an estimated 20.4 million people need EOL care yearly (WPCA, 2014). The EOL period is emotive; and can be distressing for the dying person and their families (Sousa et al., 2021; Washington et al., 2018). Death-related distress is often associated with physical and psychological uneasiness for both the patients and their loved ones (Boogaard et al., 2019; Costa-Requena et al., 2015; Hampton & Newcomb, 2018; Lo et al., 2011; Luth & Pristavec, 2020; A. J. Roth & Massie, 2007). The burdens of seeing

a dying loved one go through discomfiting illness have been associated with greater caregiver distress (Heese et al., 2013; Tilden et al., 2004).

With advancements in medical practice and patient-centered care in the United States, an increasing number of people are choosing to spend their final days in the community, away from acute hospital settings, thus, resulting in more home deaths and increasing hospice use (Chino et al., 2018). Meanwhile, studies have shown that many family caregivers report a poor understanding of the physical signs that occur in the last days and hours

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of life (Plonk & Arnold, 2005). As a result, families of dying patients often ask clinicians questions relating to EOL prognostication. Some of the commonly asked questions include: “how long does the patient have?,” “what signs will indicate the last days and hours of life are imminent?,” “Getting answers to the above questions often help the terminally-ill person and their families prepare for the impending loss, and also allows time for family members to reach out to other relatives who might want to be at the dying person’s bedside.

However, literature evidence reveals that clinicians are often inaccurate when addressing questions about prognostication in patients approaching EOL (Christakis et al., 2000; Hui, 2015; Hui et al., 2016). Healthcare providers (HCPs) frequently appear to inaccurately estimate survival (Glare et al., 2003; Moretti et al., 2021; Sagberg et al., 2022; White et al., 2016). Many HCPs involved in the care of dying patients sometimes express challenges in knowing when and how to withdraw or stop non-beneficial investigations and futile treatments that mainly prolong undue suffering for the dying persons (Clarke et al., 2003; Frost et al., 2011). The uncertainty of clinicians about survival prediction frequently leads to holding back communications with family surrogates. Hence, in the final days of life, many dying patients sometimes get inundated with unnecessary invasive and aggressive interventions that have no proven benefits, and potentially add to patients’ distress (Clarke et al., 2003; Robinson et al., 2014).

Therefore, the ability of HCPs in making timely and accurate predictions of imminent death is pivotal for clinical decision-making (Hui et al., 2009). Systematic review evidence reveals that combinations of the patient’s performance status with clinical signs and symptoms along with the clinician’s estimate provide a more accurate guide for survival prediction in terminally-ill patients (E. Chow et al., 2001). Hence, this study explores the medical literature to review the clinical signs and symptoms of imminent EOL in individuals with advanced illness and discusses the role of prognostic tools in aiding the prediction of impending death. This review provides increased knowledge and awareness for HCPs, particularly those without specialty training in palliative-hospice care, to recognize clinical signs of impending death, facilitate communication with patients and families regarding the process of death and dying, and help enhance their capability in providing more accurate survival predictions.

Methods

Systematic, comprehensive searches were conducted across medical databases including Embase, Medline, CINAHL, PsycInfo, and Google Scholar from 1992 to 2022 for relevant peer-reviewed, original papers written in or translated into English language. Broad search (MeSH) terms used to identify studies were “signs and symptoms of end-of-life in dying adults” “clinical signs of end-of-life in adults with terminal illness,”

“trajectories of signs and symptoms in individuals approaching end of life,” “prognostic tools that indicate imminent end-of-life in individuals with chronic illness,” “end of life symptoms and signs in people with advanced illness,” “clinical signs and symptoms of impending death in terminally-ill individuals from cancer and non-cancer illness.” The search yielded 185 relevant papers but only a small number of articles were directly related to the clinical signs and symptoms of an impending EOL. Citations from all the relevant studies were also reviewed to obtain additional publications. Only studies that investigated signs and/or symptoms of impending EOL in terminally-ill individuals and those that discussed prognostic tools for EOL were selected for review. Books, review articles in specialist journals, and other less formal literature also contributed to this review.

Concepts and Definitions of EOL

The term “EOL” has varying meanings across medical literature and among HCPs and policymakers (Browne et al., 2021; Froggatt & Payne, 2006; Huffman & Harmer, 2019, 2022). General Medical Council (United Kingdom) defines EOL as the period when a person with an advanced, progressive, or incurable condition is expected to die within 12 months (Bell, 2010). European Society for Medical Oncology (ESMO) Clinical Practice Guideline (CPG) refers to EOL care as “*care for people with advanced disease once they have reached a point of rapid physical decline, typically the last few weeks or months before an inevitable death as a natural result of a disease*” (Crawford et al., 2021). Several other medical literature describe EOL as synonymous with the “dying process,” “actively dying,” “terminally ill” and focuses on the last weeks, days, hours, or minutes of life (Huffman & Harmer, 2022; Hui, Nooruddin et al., 2014).

According to the National Institute on Aging, EOL care is a form of palliative or hospice care that describe the support and medical care given during the time surrounding death, with a focus on providing symptomatic relief for the dying person by identifying, assessing, and treating pain and other distressing physical signs and symptoms, along with emotional, social, and spiritual support tailored to the needs and wishes of the dying individual and their loved ones (NIH, 2021). While some terminally ill people who die from cancer and non-cancer illness may receive EOL care for several months, others may receive it for days or hours before death.

Regardless of the duration of EOL care, mitigating the stress and suffering of a dying person may contribute toward having a good death. A good death is described as person-centered EOL care that controls distressing physical symptoms, provides emotional and spiritual support, and honors the dying person’s ability to die in a place of their choosing where their dignity and privacy are respected, and measures that increase suffering and needlessly prolong life without an added quality are avoided (R. Smith, 2000).

Clinical Signs and Symptoms That Show EOL is Imminent in Individuals With Advanced Illness

The period at which terminally-ill individuals transition from active participation in the activities of daily living to experiencing progressive worsening of underlying illness has been described as the “transitional phase” of the dying process (Doyle-Brown, 2000). This period commonly chronicles the trend of events in the last weeks to days of life. Depending on the underlying illness, terminally-ill individuals may present with complex symptoms burden that lead to physical decline, multiple unplanned hospital admissions, and decreased response to treatment, among others. Anecdotal evidence shows that terminally-ill individuals with rapidly declining functional status usually gravitate toward accelerated progression to EOL within days or weeks. Thus, having a good understanding of chronic illness trajectory generally provides a useful guide for clinicians to project an overall survival/future decline estimate (Lynn & Adamson, 2003).

As the chronic illness progresses, the terminally-ill person may present with worsening symptoms and signs relating to losing appetite for foods, dysphagia, refractory fatigue, incontinence, oliguria, intractable pain, decreased communications, increasing dyspnea, refractory nausea and vomiting, excessive respiratory secretions, altered consciousness, confusion, agitation, restlessness, terminal delirium among others (E. Bruera et al., 1992; Levenson et al., 2000; Lichter & Hunt, 1990; Plonk & Arnold, 2005; Quinn & Thomas, 2017). One study that compared the trajectories of physical signs and symptoms among hospitalized young-old and the oldest-old patients showed similarities in the last days of life (Steindal et al., 2013).

Hui et al. (Hui, Dos Santos et al., 2014) conducted a prospective observational study on 357 patients dying from advanced cancer, to explore the frequency and onset of 10 bedside physical signs, and their likelihood ratios of association with death within 3 days. The 10 highly specific clinical signs studied included apnea periods, Cheyne-Stokes breathing, death rattle, dysphagia of liquids, impaired consciousness, Palliative Performance Scale (PPS) $\leq 20\%$, peripheral cyanosis, absence of radial artery pulse, respiration with mandibular movement, and decreased urine output to < 100 mL. The authors analyzed the occurrence of these physical signs over the last 12 hr of life, and findings demonstrated that decreased urine output, absence of radial artery pulse, apnea periods, Cheyne-Stokes breathing, death rattle, breathing with mandibular movement, and peripheral cyanosis had high specificity and high likelihood ratios for impending death within 3 days (Hui, Dos Santos et al., 2014).

In a subsequent study conducted by Hui et al. (Hui et al., 2015), they reported the frequency and onset of additional eight bedside clinical signs that were found to be highly diagnostic of imminent death in terminally-ill

patients. These bedside signs include nonreactive pupils, decreased response to visual stimuli, inability to close eyelids, decreased response to verbal stimuli, drooping of the nasolabial fold, hyperextension of the neck, grunting of vocal cords, and upper gastrointestinal bleeding. According to Hui et al, these eight clinical signs occur in 5% to 78% of dying cancer patients and had high specificity ($>95\%$) and a high positive likelihood ratio for death occurring within 3 days (Hui et al., 2015). One recently published prospective observational study buttresses the findings of Hui et al. by demonstrating that pulselessness of the radial artery, breathing with mandibular movement, decreased response to verbal stimuli, and decreased response to visual stimuli show high accuracy in predicting death within 7 days in terminally-ill non-cancer individuals (Hosoi et al., 2021).

Similarly, a multi-site cohort study across 23 inpatient hospice units comprising 1,396 advanced cancer patients with palliative performance score $\leq 20\%$ was followed-up until death to explore clinical signs that predict death within 3 days. Findings demonstrated that 80% of patients who had urine output ≤ 200 ml/day and decreased response to verbal stimuli died within 3 days, and 53% of all patients who had urine output ≤ 200 ml/day but no decreased response to verbal stimuli died within 3 days (Mori et al., 2021).

Kehl and Kowalkowski conducted a systematic review study that analyzed data representing 2,416 patients from multiple settings on the prevalence of signs and symptoms of imminent death. They reported highest prevalence of dyspnea (56.7%), pain (52.4%), respiratory secretions/death rattle (51.4%), and confusion (50.1%) in the last 2 weeks of life (Kehl & Kowalkowski, 2013). Goodridge et al. affirmed that distressing dyspnea is a more common sign of EOL within the last 72 hr before death (Goodridge et al., 2005).

One prospective observational study involving 181 terminal-ill cancer patients, who died in a palliative care unit, evaluated the observed events that herald the onset of the dying process. The study demonstrated that a confused mental state; decreased consciousness level, death rattle, decreased blood pressure, and low oxygen saturation are some of the significant changes that occurred in the 48 hr preceding death (Hwang et al., 2013). While vital sign changes alone are not reliable means to predict imminent death, available evidence shows that significant drops in baseline blood pressure and oxygen saturation frequently occur in the last hours to days of life (S. Bruera et al., 2014).

Decreased Food Intake and Impaired Hydration

Terminally-ill individuals nearing EOL often refuse to eat and drink due to lack of appetite (NHS, 2020). This period may heighten anxiety and cause distress for family caregivers as they become terrified about facing the reality of an impending loss of their loved one. The situation becomes even more difficult as the general health

of the terminally-ill person continues to decline despite active treatments, and family surrogates struggle with choosing between focusing on comfort measures care or continuing “futile” aggressive interventions that tend to prolong suffering for the dying person (Melin-Johansson et al., 2012). Refusal of food and fluid by a dying person is a common occurrence, particularly as the body slowly shuts down, and this may be the evidence signifying an actively dying process rather than starvation (Ijaopo & Ijaopo, 2019). Previous studies have argued that dehydration is not distressing, rather, may provide comfort to the dying patient in reducing death rattle (Regnard & Mannix, 1991). One recently published multicenter prospective observational study showed that giving a dying person a higher amount of fluids, in excess of 250 mL/day, during 48 to 25 hr before death may be associated with the occurrence of terminal restlessness in the last 24 hr of life (Lokker et al., 2021). Hence, when a terminally-ill individual starts refusing to eat or drink as they approach the EOL period, it is important to provide appropriate education and support for family caregivers, explore any prior advance directives and explain to families that the most available research evidence and experts’ recommendations agree that careful (comfort) hand feeding as tolerated is the recommended standard of care (American Geriatrics Society Ethics Committee and Clinical Practice and Models of Care Committee, 2014; Druml et al., 2016; Palecek et al., 2010; Schwartz et al., 2021; S. A. Smith & Andrews, 2000; van de Vathorst, 2014).

Intractable Pain

Literature evidence shows that terminally-ill individuals may experience high burden of intractable pain and other distressing symptoms as they approach the final moments of life (Davidoff et al., 2021; Drageset et al., 2014; Saphire et al., 2020). International Association for the Study of Pain (IASP) Subcommittee on Taxonomy defined pain as “*an unpleasant sensory and emotional experience associated with actual or potential tissue damage or is described in terms of such damage*” (Raja et al., 2020). Intractable pain near the EOL is discomforting for both the dying person and families, and may also exacerbate other symptoms (Rome et al., 2011). One systematic review study reports pain management as the most identified worry faced by family caregivers in EOL care (Chi & Demiris, 2017). Another study reports that pain was the most prevalent symptom burden (52%), followed by agitation (35%) and shortness of breath (35%) among nursing home residents dying from dementia in the last week of life (Hendriks et al., 2014).

The inability of an individual to verbally report pain does not necessarily negate the possibility of experiencing pain. Intractable pain in non-communicative individuals approaching EOL may present with nonverbal cues of pain that include agitation, restlessness,

grimacing, guarding, moaning, crying, shouting, tense or rigid body, short, rapid breathing, and unexplained sweating, among others (McGuire et al., 2016). Identifying and treating pain in both communicative and non-communicative patients is an integral aspect of EOL care. Clinical and research evidence show that opioids are effective for intractable pain management in terminally-ill individuals and should be chosen for moderate or severe pain in line with the World Health Organization pain ladder (Clary & Lawson, 2009; Hänninen et al., 2013). A study finds that on the day of death, 77% of dying nursing home residents received opioids, with a median of 90 mg/24 hr (oral equivalents) (Hendriks et al., 2014).

Terminal Delirium

Terminal delirium is a frequently observed bedside indicator of an impending EOL that exert a profoundly negative impact on the dying person and their family. Studies show terminal delirium is experienced by almost 85% to 88% of people in the last week to days of life (Breitbart et al., 2002; Keeley, 2009). The best evidence suggests that almost all actively dying persons will have a subtype of (hypoactive or hyperactive) delirium in the days to hours before death (Lawlor & Bruera, 2002). In terminally-ill people, delirium syndrome usually involves multifactorial causes. The most recent evidence from prospective observational studies, systematic reviews and meta-analysis studies report risk factors for terminal delirium to include older age, male sex, organ failure, fluid and electrolyte imbalances, dehydration, suboptimal pain management, hypoxia, breathlessness, poor well-being with declining performance status, and medication adverse effects (Bush et al., 2014; Corli et al., 2021; Ellsworth et al., 2021; Guo et al., 2021). Delirium care poses a significant challenge in EOL care, causing significant distress for the dying person and families, as it is often under-diagnosed or undetected. Thus, this results in patients being inappropriately treated or untreated (Breitbart & Alici, 2008; Moyer, 2011). It is therefore paramount for clinicians to properly identify the clinical signs of delirium in terminally-ill patients and use effective measures of non-pharmacologic and pharmacologic interventions as appropriate to mitigate the distressing problems (Breitbart & Strout, 2000; Corli et al., 2021; Finucane et al., 2020; Hui, 2019). As a dying individual approaches the EOL, treating refractory terminal delirium to mitigate suffering may sometimes require the use of palliative sedation (Arantzamendi et al., 2021; Patel et al., 2019). Palliative sedation, although controversial (Raus et al., 2016; Vitale et al., 2019) has been shown from systematic research evidence not to hasten death (Beller et al., 2015). Before commencing palliative sedation, reviewing the dying person’s advance care planning and obtaining progressive consent through effective

communication with family surrogates to promote shared decision-making are of primary importance, as this help to increase trust and confidence in healthcare providers (Miccinesi et al., 2017; Namba et al., 2007; Virdun et al., 2015; Waller et al., 2020).

Death Rattle

Another frequently observed bedside sign that may signal impending EOL is known as death rattle. It occurs from noisy breathing caused by the accumulation of mucus secretions in the respiratory tract, and may potentially lead to breathing discomfort for the dying person (Lokker et al., 2014). This noisy breathing often causes psychological distress to families, since dying persons are often unconscious when they experience death rattle (Watts et al., 1997). Studies have shown that death rattle occurs in 25%–50% of people who are imminently dying (Lokker et al., 2021; Morita et al., 2004). However, one study found that 92% of terminally-ill patients developed death rattle in the final days of life (Ellershaw et al., 1995). Death rattle is a strong predictor of imminent death, and nearly 80% of people die within 48 hours after its onset (Wildiers & Menten, 2002). Generally, the distress from death rattle is frequently managed by repositioning and clearing the upper airways of fluid via mechanical suctioning or with anticholinergic drugs (Wee & Hillier, 2008). Research studies reveal there are no significant differences in the effectiveness or survival time among atropine, hyoscine butylbromide, and scopolamine in the treatment of death rattle (Wildiers et al., 2009).

Respiration With Mandibular Movement (RMM)

Clinical evidence shows respiration with mandibular movement (RMM) as one of the highly specific bedside clinical signs of impending death. RMM is an abnormal breathing pattern where breathing becomes very shallow, and the mouth opens as a result of periodic mandibular jaw movement that occurs during inspiration. RMM may be associated with gasping and period of apnea between breaths. One prospective observational study conducted over a 3-year period to determine timing and variations in clinical findings in the final days and hours before death in older adults with advanced illness demonstrated consistent findings of RMM at 12 hr before death (Matsunami et al., 2018). Similarly, a recently published multicenter prospective cohort study of 1,526 dying cancer patients that explored the natural course of RMM showed that 1,065 (69.8%) of dying patients had RMM at the end of life. Among them, 14.8% of the patients died within 30 min from RMM onset, 14.3% within 30 to 60 min, 34.4% within 1 to 4 hr, 17.5% within 4 to 12 hr, and 8.9% within 12 to 24 hr. The authors concluded that 80% of dying patients

experienced RMM within 12 hr of death (Kaneishi et al., 2022). It is therefore important to educate the caregiver(s) of a dying person that RMM is part of the physiological changes associated with the dying process. Pharmacologic approaches may be utilized for optimizing comfort measure care, particularly when there is an associated dyspnea and/or pain (Saphire et al., 2020).

End-of-Life Dreams and Visions (ELDVs)

Not uncommonly, actively dying individuals, regardless of their socio-economic status and cultural background may report having dreams or some visual hallucinations where they report seeing deceased loved ones, friends, and/or family members who were long dead (Depner et al., 2020; Nosek et al., 2015; Nyblom et al., 2022; Shinar & Marks, 2015). These ELDVs may be associated with joy/excitement or trigger increased fear and anxiety for both the dying individual and their family (Kerr et al., 2014; Levy et al., 2020). Many HCPs believed these strange experiences occur regardless of the underlying illness and are not related to medication adverse effects (Pan et al., 2021; Santos et al., 2017). Previously, clinicians have claimed ELDVs are variants of delirium presentation associated with the EOL period (Breitbart & Alici, 2008). However, in most instances, the affected individuals report that their experience felt real (Dam, 2016; Fenwick et al., 2010; P. Grant et al., 2014). Research studies have also shown that affected individuals with ELDVs often demonstrate organized thoughts with no breakdown of awareness, attention, and concentration (Depner et al., 2020; Kerr et al., 2014; Santos et al., 2017). It is estimated that nearly 50-70% of dying people experience ELDVs (Dam, 2016; Mazzarino-Willett, 2010). While ELDVs often occur when death is imminent within days or hours before death, it is often non-specific and may also occur about weeks or months before death (Depner et al., 2020; Kerr et al., 2014; Levy et al., 2020; Nyblom et al., 2022; Santos et al., 2017). Grant et al. (Grant et al., 2021) report that providing education for patient and family that focuses on awareness and understanding of ELDVs may promote better bereavement outcomes for family members.

Terminal Lucidity

Terminal lucidity is sometimes noted by those caring for the dying. This is a period when a critically-ill person transiently experiences increased alertness, energy surge, and an unexpected return of mental clarity and memory functioning shortly before death (Koczanowicz, 2020; Nahm et al., 2012). This period of energy surge before death can occur days, hours, or minutes before death (Lim et al., 2018). Terminal lucidity has been reported in dying individuals from advanced dementia, strokes, and mental illnesses, such as schizophrenia (Bostanciklioğlu,

2021; Nahm, 2009). The dying person, who often is less responsive or even comatose at this period, suddenly becomes awake and alert with unexplained increased energy and may engage in meaningful conversation and/or request to eat or drink. Studies showed that 84% of people who experience terminal lucidity usually die within a week, with 43% dying within 24 hr (Nahm, 2009). While medical research on terminal lucidity is scanty (Chiriboga-Oleszczak, 2017), available studies claimed anecdotal reports of people experiencing terminal lucidity in the medical literature dated back more than 250 years (Nahm et al., 2012). Proper awareness of these unusual EOL experiences can help clinicians and family members get prepared for such occurrences. Providing appropriate education to family caregivers enables them to treasure that last moment with their dying loved ones by creating good memories, and at the same dissuades them from embracing any false hope that the dying person has started to improve.

Importantly, HCPs must have the necessary skills in identifying the physical signs and symptoms of impending EOL in terminally-ill patients and facilitate effective communication about EOL care with the family caregivers and/or patient as appropriate. Fear of prognostic certainty or afraid of causing distress to patients or families should not be a barrier to initiating EOL discussions. Clinical studies demonstrate evidence of significant benefits when clinicians engage in early EOL care discussions with terminally-ill patients and/or their surrogates (Brighton & Bristowe, 2016; Gauthier, 2008). Table 1 below shows wide-ranging lists of common clinical signs that may indicate impending EOL and the estimated time before death.

Comparison of EOL Signs and Symptoms in Cancer Versus Non-cancer Disease

Diseases in the adults' population that may progress to terminal phases are often due to advanced cancer, neurological diseases (such as dementia, stroke, Parkinson's disease, multiple sclerosis, and motor neuron disease), end-stage organ failure, as well as severe frailty from old age, osteoporosis, malnutrition and HIV/AIDS (Chiu et al., 2021; Lunney et al., 2003; Lynn & Adamson, 2003; Murray et al., 2005). Over the years, medical experts and researchers from across different specialties have conducted studies to compare trajectories of clinical signs and symptoms in dying individuals with advanced cancer versus non-cancer-related diseases. A large cohort study from four US regions, involving 14,456 participants, aged 65 years or older, interviewed in the last year of their lives determined if trajectories of functional decline differ among four types of illness (sudden death, cancer death, death from organ failure, and frailty). Findings demonstrated that trajectories of functional decline at the EOL are variable depending on the underlying disease. While people who died from

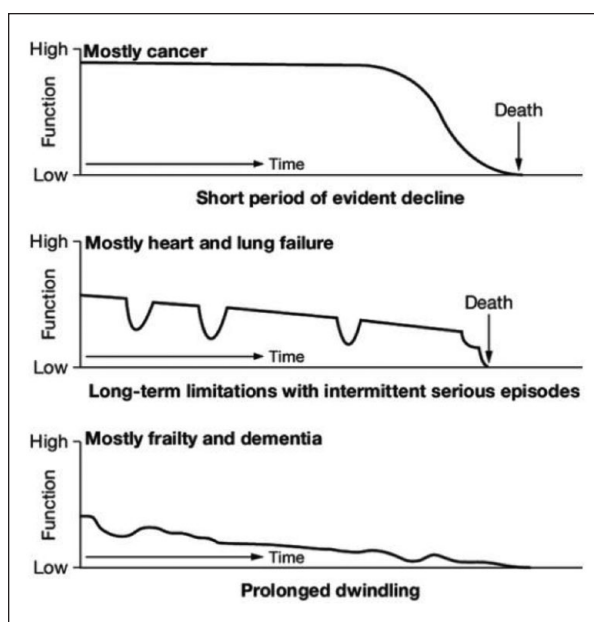


Figure 1. The common illness trajectories for cancer and non-cancer illness. Extracted from Lynn and Adamson (2003). With permission from RAND Corporation, Santa Monica, California, USA.

cancer disease were functional early in the final year of life, they became significantly disabled 3 months before death. Organ failure decedents experienced a more fluctuating pattern of decline, with considerably poorer function during the last 3 months before death. However, frailty decedents were remarkably more disabled in the final year and dependent during the last month before death (Lunney et al., 2003). Figure 1 below shows the common illness trajectories for cancer and non-cancer disease individuals.

Evidently, studies show that as terminally-ill people from either advanced cancer or non-cancer disease approach the last week to days and hours of life, they manifest comparable emotional distress and symptom burden (Claessens et al., 2000; Steinhauer et al., 2011; Wysham et al., 2015). Data analysis study of 1,883 Health and Retirement Study (HRS) participants, involving community-dwelling adults aged 51 years or older, between 2000 and 2010 compared the EOL experiences of adults who died of end-stage renal disease (ESRD) with those that died from advanced cancer. Findings revealed that people dying of ESRD and advanced cancer had similarly high burdens of signs and symptoms that included moderate-to-severe pain, frequent vomiting, dyspnea, depression, and altered mental status at the EOL (Wachterman et al., 2017). Likewise, a large-scale systematic review analysis of 64 original studies that compared symptom prevalence in people with markedly advanced cancer, AIDS, heart disease, chronic pulmonary disease, and renal disease concluded that the common pathway toward death is similar for both cancerous and non-cancerous diseases (Solano et al., 2006).

Table 1. Clinical Signs and Their Estimated Time Before Death in Terminally-ill Individuals.

<1 to 3 days Before Death	>3 to 7 days Before Death	>7 to 28 days Before Death
Death rattle (Terminal respiratory secretions) (Hui, Dos Santos et al., 2014; Wildiers & Menten, 2002)	Decreased level of consciousness (Matsunami et al., 2018)	↓Food intake/Loss of Appetite (Matsunami et al., 2018)
Respiratory breathing with mandibular movement (Hui, Dos Santos et al., 2014; Kaneishi et al., 2022)	Agitation/Purposeless movement (Hui et al., 2015)	Dysphagia to solid (Hui, Dos Santos et al., 2014)
Cheyne-Stokes breathing (Goodridge et al., 2005; Hui, Dos Santos et al., 2014)	Dysphagia to liquids (Hui, Dos Santos et al., 2014)	Intractable pain (Hendriks et al., 2014)
Absence of radial artery pulse (Hui, Dos Santos et al., 2014)	Mottling (Hui et al., 2015)	Dyspnea (Kehl & Kowalkowski, 2013)
Urine output less than 200 ml/day (Hui, Dos Santos et al., 2014; Mori et al., 2021)	↓response to verbal stimuli (Hosoi et al., 2021)	Delirium/Impaired consciousness (Breitbart & Alici, 2008; Matsunami et al., 2018)
Non-reactive pupils (Hui et al., 2015)	↓response to visual stimuli (Hosoi et al., 2021)	Cold/Cool extremities (Hui et al., 2015; Hui, Dos Santos et al., 2014)
Grunting of vocal cords (Hui et al., 2015)	Capillary refill >3 s (Hui et al., 2015)	Refractory fatigue and weakness (Plonk & Arnold, 2005)
Peripheral cyanosis (Hui, Dos Santos et al., 2014)	Decreased speech (Hui et al., 2015)	Declining functional status/↑ frailty (Levenson et al., 2000)
Terminal restlessness (terminal delirium) (Lokker et al., 2021)	Irregular breathing pattern (Hui et al., 2015)	Depression (Plonk & Arnold, 2005)
Hyperextension of the neck (Hui et al., 2015)	Rapid decline to palliative performance score of 20% (Prompantakorn et al., 2021)	Rapid decline to palliative performance score of 30-40% (Baik et al., 2018; Harrold et al., 2005; Prompantakorn et al., 2021)
Blood pressure (systolic <100mmHg with ↓ ≥20mmHg and diastolic <60mmHg with ↓ ≥10mmHg) (S. Bruera et al., 2014)	↓ systolic blood pressure <100mmHg; oxygen saturation <90% and Temperature <36°C (Hui et al., 2015)	Combination of cognitive failure, dysphagia, and weight loss >10% of baseline (E. Bruera et al., 1992)
Blood pressure <80mmHg systolic (Hwang et al., 2013)	Myoclonus (Hui et al., 2015)	Decreased breath sounds (Hui et al., 2015)
Inability to close eyelids (Hui et al., 2015; Hui, Dos Santos et al., 2014)	Upper gastrointestinal bleeding (Hui et al., 2015)	↓ response to treatment (Quinn & Thomas, 2017)
Drooping of the nasolabial fold (Hui et al., 2015)		Peripheral edema (Hui et al., 2015)
Rapid decline to palliative performance score of 10% (Baik et al., 2018; Hui, Dos Santos et al., 2014; Prompantakorn et al., 2021)		

Several other studies also report that terminally-ill patients from non-cancer diseases approaching EOL suffer comparably high burdens of disease similar to those dying from advanced cancer (Gore et al., 2000; Lastrucci et al., 2018; Mizuno et al., 2021; Murray et al., 2002; Prabhu et al., 2021; K. Roth et al., 2000). However, the former group frequently gets subjected to burdensome aggressive interventions, has underutilization of palliative care services, and patients and their surrogates often get late discussions about EOL care compared with patients who have advanced cancer (Gore et al., 2000; Lastrucci et al., 2018; Mizuno et al., 2021; K. Roth et al., 2000).

Prognostic Tools for EOL Prediction

The ability of clinicians to provide prognostic information is important to patients and families, and essential

in clinical decision-making. However, many HCPs have expressed challenges in talking to patients and families about EOL care due to a limited understanding of using prognostication tools in identifying terminally-ill non-cancer patients nearing the EOL (Pocock et al., 2019). This problem often culminates in instituting potentially non-beneficial treatments and aggressive interventions that appear to prolong the suffering of the dying individuals, as well as causing undue anxiety and distress for families.

Several reliable and valid tools are widely used in palliative and hospice care medicine for assessing functional performance and predicting survival in patients with advanced illness (Simmons et al., 2017). The commonly used tools which include the Palliative Performance Scale (PPS), Karnofsky Performance Status (KPS), Eastern Cooperative Oncology Group

(ECOG) Performance Status, Palliative Prognostic Score, Palliative Prognostic Index, and the Glasgow Prognostic Score, are reliable and validated tools that can be used by HCPs in any healthcare settings (Chu et al., 2019; Mei et al., 2013; Péus et al., 2013; Simmons et al., 2017). Available research evidence shows that these tools, particularly PPS, correlate well with actual survival and median survival time for terminally-ill patients from cancer and non-cancer disease. The lower the score, the worse the survival for most terminal illnesses (Anderson et al., 1996; Harrold et al., 2005; Morita et al., 1999; Virik & Glare, 2002).

A systematic review and meta-analysis by Chow et al. on inter-rater reliability in performance status assessment among healthcare professionals demonstrate a notable correlation between performance status scores, with no one tool statistically superior to the others (R. Chow et al., 2020). In the United States, PPS, a modified version of KPS, is one of the most commonly used tools for evaluating patients' performance and survival status in palliative and hospice care settings (Anderson et al., 1996; Harrold et al., 2005). PPS uses five observer-rated domains that include: ambulation; activity and extent of disease; self-care, intake; and conscious level. Each of these (five) domains is classified into 11 categories based on 10%-point interval scores which range from 0% to 100%, with a PPS score of 0% indicating death and 100% score representing being fully mobile and healthy (see Table 2). Studies reveal that the PPS score is a strong predictor of survival in palliative and hospice patients (Lau et al., 2006), and survival days do not differ by racial/ethnicity group, however, younger patients and women appear to survive longer than older patients and men respectively (Lau et al., 2006; Weng et al., 2009).

One prospective cohort study conducted at a large community hospice program involving all 466 patients enrolled in hospice during the study period evaluated the prognostic value of PPS as a predictor of mortality. Investigators recorded each patient's PPS score at the time of enrollment and patients were followed up until death or discharged from hospice. Findings showed that 6-month mortality rates for 3 PPS categories were 96% (for PPS scores 10-20%), 89% (for PPS scores 30%-40%), and 81% (for PPS scores 50 or above) (Harrold et al., 2005).

More recently, a retrospective cohort study investigated the associations between PPS and survival time among 407 adults (with cancer and non-cancer illness) who received palliative care consultation in an acute hospital setting over a 2-year period. Findings showed PPS and survival time in cancer patients were significantly correlated. Cancer patients with PPS 10%, 20%, 30%, 40 to 60%, and 70% to 80% had a median survival time of 2, 6, 13, 39, and 95 days respectively, while non-cancer patients with PPS 10%, 20%, and 30% had a median survival time of 8, 6, and 24 days, respectively (Prompantakorn et al., 2021). Another systematic review

of 17 studies, comprising nine studies with cancer diagnoses (15,257 participants) and eight mixed diagnoses (129,781 participants) conducted across various healthcare settings including Canada and United States, analyzed how the PPS tool has been used to estimate survival at the EOL. The authors reported that survival estimates ranged from 1 to 3 days for patients with PPS scores of 10% compared with 5 to 36 days for those with PPS scores of 30%. All 17 studies demonstrated that PPS was a significant predictor of survival time or mortality rate among palliative care patients with mixed diagnoses and advanced cancer disease (Baik et al., 2018).

Assessment measures through the use of prognostic tools provide a helpful reference for HCPs in timing the goals-of-care discussion with patients and families, and in determining hospice appropriateness when a patient is transitioning toward the EOL period (Jansen et al., 2015; Olajide et al., 2007).

Research evidence demonstrates that using a prognostic tool provides a more accurate prediction of survival than Clinicians' prediction of survival (Hui et al., 2016). In addition, the use of prognostic tools to estimate survival time may provide reliable, valid, and potentially useful information that can guide patient care (Lynn et al., 1995).

The ability of clinicians to identify the clinical signs of imminent end-of-life in terminally-ill individuals is essential for providing better EOL care and also helps promote shared decision-making for EOL care that is tailored to meet the dying individual's physical, psychological, social, and spiritual needs.

Implications for Clinical Practice

In any terminally-ill individual undergoing a progressive decline, it is imperative for HCPs to have the necessary skills for identifying the physical signs of impending EOL as discussed in this review, and initiate discussions with the dying person (if possible) and family surrogates about the naturalness of dying and the limitations of medical interventions. During discussions, HCPs must use clear terms, such as, the patient is dying and will die, particularly when clinical evidence shows the patient is actively dying. Clinicians should avoid using ambiguous statements such as "patient may not improve" "your loved one's illness is very serious" and "prognosis is guarded." The use of these statements may cause misguided assumptions or lack clarities to adequately inform patients/families about the impending death. Anecdotal clinical experience shows that families of dying patients can cling to any news that gives them the slightest ray of hope during EOL discussions. The well-intentioned but erroneous decision by HCPs to censor the information provided to patients and families in an attempt to not give potentially hurtful and sad news of impending death may lead to providing inaccurate and misleading information that may falsely raise the hopes

Table 2. Palliative Performance Scale (PPS) Showing The Estimated Median Survival in Days.

%	Ambulation	Activity Level <i>Evidence of Disease</i>	Self-Care	Intake	Level of Consciousness	Estimated Median Survival in Days		
						A	B	C
100	Full	Normal <i>No Disease</i>	Full	Normal	Full	N/A	N/A	108
90	Full	Normal <i>Some Disease</i>	Full	Normal	Full			
80	Full	Normal with Effort <i>Some Disease</i>	Full	Normal or Reduced	Full			
70	Reduced	Can't do normal job or work <i>Some Disease</i>	Full	Normal or Reduced	Full	145		
60	Reduced	Can't do hobbies/ housework <i>Significant Disease</i>	Occasional Assistance Needed	Normal or Reduced	Full or Confusion	29	4	
50	Mainly sit/Lie	Can't do any work <i>Extensive disease</i>	Considerable Assistance Needed	Normal or Reduced	Full or Confusion	30	11	41
40	Mainly in Bed	Can't do any work <i>Extensive disease</i>	Mainly Assistance	Normal or Reduced	Full or Drowsy or Confusion	18	8	
30	Bed Bound	Can't do any work <i>Extensive disease</i>	Total Care	Reduced	Full or Drowsy or Confusion	8	5	
20	Bed Bound	Can't do any work <i>Extensive disease</i>	Total Care	Minimal sips	Full or Drowsy or Confusion	4	2	6
10	Bed Bound	Can't do any work <i>Extensive disease</i>	Total Care	Mouth care only	Drowsy or Coma	1	1	
0	Death	0	-	-	-	-	-	-

Note. (A) Survival post-admission to an inpatient palliative unit, all diagnoses (Virik & Glare, 2002). (B) Days until inpatient death following admission to an acute hospice unit, diagnoses not specified (Anderson et al., 1996). (C) Survival post-admission to an inpatient palliative unit, cancer patients only (Morita et al., 1999).

of the dying person and their families (Fallowfield et al., 2002).

More importantly, where palliative-hospice care service is available, involving them in the goals of care discussions and in helping to provide symptomatic treatment and comfort measures care may help improve the overall quality of EOL care for the dying individual. A report from Lancet Commission on Palliative Care and Pain Relief approximated that 90% of people dying from terminal illnesses across the world face serious health-related distress that would benefit from palliative care (Knaul et al., 2018). Thus, it is essential that palliative and hospice care services be made available to all dying patients at all healthcare levels. Regrettably, studies have shown that palliative and hospice care services for EOL care are among the most neglected dimensions of global health (Horton, 2018). Providing comprehensive care that alleviates signs and symptoms of distress associated with a terminal illness is the fundamental goal of palliative and hospice care services.

Conclusion

A good understanding of the bedside signs and symptoms of imminent EOL combined with the use of prognostic tool assessment enhances the clinician's capability

to provide a more accurate survival prediction, diagnose impending death, and help facilitate communication with patients and families about the EOL process. These signs may include obtaining history of the underlying illness getting progressively worse, rapid decline in performance status, multiple unplanned hospital admissions, decreasing response to treatment, and other complex signs and symptoms burden, such as refusal of foods and fluids, intractable pain, increasing dyspnea despite optimal treatment interventions, impaired consciousness, oliguria, terminal agitation and restlessness, skin mottling, death rattle, RMM, Cheyne-Stokes breathing, among others.

While it may be difficult to accurately predict the timing of death, having the ability to identify the signs and symptoms of impending death in terminally-ill individuals may lead to an early anticipation of care needs and better planning to provide care that is tailored to the individual's needs, and ultimately results in better EOL care, as well as a better bereavement adjustment experience for the families. Published studies also demonstrate that dying persons are protected from death anxiety when they were able to prepare for the EOL (Tang et al., 2021).

Future research to evaluate the signs and symptoms of impending EOL in individuals with advanced illness is highly encouraged.

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