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# Prevalence of Ethical Issues in Patients with Advanced Cancer: Secondary Analysis of Pooled Data from the Development and Validation Cohorts of the PALCOM Scale for Complexity of Palliative Care Needs

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**Simple Summary:** The experience of individuals with incurable cancer and a limited life expectancy is profoundly complex. Ethical issues arise when the commonly accepted guiding principles of healthcare conflict or are interpreted differently by the various individuals involved in the decision-making process in a specific situation. Our study, based on a pooled analysis of two prospective cohorts of advanced cancer patients, confirmed a high prevalence of patients facing ethical issues. Most of these issues were primarily related to the proportionality of healthcare interventions, patient information, or the desire to hasten death. It is important to highlight that ethical issues were associated with greater complexity of palliative care needs, and their prevalence decreased after the baseline visit, suggesting that early identification and intervention can improve outcomes**.** Ethical issues can cause significant distress for patients, their families, and the care team. All the issues observed in this study were directly or indirectly related to decision-making and the recognition of patient autonomy. Based on these findings, it is crucial to strengthen basic competencies in clinical ethics and communication skills among healthcare professionals. This approach would enable the early identification of ethical issues, facilitate measured interventions, and improve supportive care outcomes.

**Abstract:** *Introduction:* The life experience of patients with advanced cancer and limited life expectancy is unique and profoundly complex, often leading to moral discrepancies among the various individuals involved in decision-making. There is no data in the literature on the prevalence of ethical issues in the end-of-life care of patients with advanced cancer. *Objectives:* The primary objective of this study is to identify the overall and specific prevalence of ethical issues in the end-of-life care process for patients with advanced cancer. *Method:* We conducted a secondary analysis of pooled data from the prospective development and validation cohorts of the PALCOM scale for the complexity of palliative care needs. This was done to determine the overall and specific prevalence of ethical issues, describe their evolution over a 6-month follow-up period, and their association with the level of palliative care complexity. *Results:* A total of 607 patients with advanced cancer and a life expectancy of ≤ 6 months were included. The absence of significant differences in clinical data and

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the frequencies of the PALCOM scale domains between the development and validation cohorts, conducted in different settings and times, confirmed the reliability of the pooled data sample. Systematic application of the PALCOM scale identified 126 patients (20.7%) who experienced at least one ethical issue. A total of 204 ethical issues (1.6 per patient) were recorded, related to: proportionality of healthcare intervention (15.6%); information (13.0%); research (2.9%); desire to hasten death (1.8%); palliative sedation (0.15%). The monthly probability of presenting an ethical issue was significantly higher at the baseline visit (24.0%) compared to the rest of the 6-month follow-up period (14-17%) ($p<0.001$) The prevalence of ethical issues was significantly higher in patients with greater palliative care complexity according to the PALCOM scale: 4.5% in low complexity; 19.5% in medium complexity; 30.8% in high complexity ($p<0.001$). *Conclusions:* The prevalence of ethical issues in patients with advanced cancer is high. Most of these issues are directly or indirectly related to the preservation of patient autonomy in the decision-making process. The presence of ethical issues is significantly associated with greater complexity of palliative care needs. In this context, it is crucial for healthcare professionals to strengthen both communication skills and basic competencies to effectively identify, assess, and manage these ethical issues.

**Keywords:** advanced cancer; ethic issues; complexity of palliative care needs; early palliative care.

## Introduction

Bioethics is defined as the systematic study of the moral dimensions of life sciences and healthcare. This definition acknowledges the inherent moral nature of actions, behaviours, and health policies [1].

The life experience of patients with advanced cancer and limited survival expectancy is unique and profoundly complex. Symptomatic burden, functional decline, emotional impact, family support, social environment, spirituality, moral values, life history, cultural context, and the conditions of the patient's care setting significantly influence the coping strategy for the end-of-life process [2-5]. It is a complex process because it depends on the continuous and non-linear interaction of multiple multidimensional variables, maintaining a frequently unstable balance with not always predictable outcomes [5-13].

In the complex end-of-life scenario, the patient, family, and healthcare professionals actively participate in the decision-making process. The healthcare professional provides objective information about the disease and its treatment, based on scientific evidence. However, each patient assigns a unique and subjective value and meaning to their illness. This dynamic and inter-subjective process often leads to moral discrepancies among the various individuals involved in decision-making.

Ethical reflection emerges when the commonly accepted codes, rules, or habits guiding the decision-making process become uncertain. The widely accepted ethical principles of beneficence, autonomy, justice, and non-maleficence govern the actions of healthcare professionals [14]. Ethical issues arise when, in a specific situation, one of these principles is violated, conflicts with another, or is interpreted differently by the various individuals involved.

Published studies focus on the narrative description of ethical issues in the end-of-life process from a theoretical perspective or detail, through surveys, the most common ethical concerns among professionals [15-23]. However, the literature provides very little data on the prevalence of ethical issues in the end-of-life process in real clinical practice. In 2021, our group published the only prospective study on the prevalence of ethical dilemmas in the end-of-life process of patients with advanced cancer. This study, based on a systematic multidimensional evaluation of all patients included in the prospective cohort for the development of the PALCOM scale for complexity of palliative care needs, identified a prevalence of ethical issues of 27.8% [13].

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The PALCOM scale is a multidimensional assessment tool designed to measure the complexity of palliative needs in patients with advanced cancer. This scale comprises five assessment domains, including the identification of ethical or existential issues. In 2018, our group published a prospective cohort study that led to the creation and development of the PALCOM scale (development cohort) [9]. In 2021, we published the aforementioned secondary analysis on the prevalence of ethical issues, based exclusively on the development cohort [13]. In 2023 and 2024, we published two validation studies that used the same inclusion criteria and assessment system (validation cohort) [10,11]. At this time, we believe that conducting a pooled analysis of data from the development and validation cohorts of the PALCOM scale is timely and will help reinforce the consistency of prevalence data on ethical issues. The objective of this study is to determine the overall and specific prevalence of different ethical issues observed in the end-of-life process in patients with advanced cancer. Our hypothesis is that the prevalence of ethical issues is high, that there are no significant differences between the values observed by different teams and in different study periods (development and validation cohorts), and that the overall prevalence decreases during follow-up, likely because early detection allows for specific intervention.

## 2. Materials and Methods

We conducted a secondary analysis of the pooled data from the development and validation cohorts of the PALCOM scale, which measures the complexity of palliative needs in patients with advanced cancer. Both cohorts were prospective and multicentre, with a maximum follow-up of 6 months. They applied the same inclusion criteria and used the same methodology for both the assessment and the recording of variables.

### *2.1. Setting and Study Periods*

The development cohort, aimed at constructing a model for complexity of palliative care needs (PALCOM scale), included patients from November 2012 to January 2013. The validation cohort, aimed at confirming the consistency and predictive value of the PALCOM scale, included patients from December 2020 to April 2021. Both studies involved multiple public healthcare centres across all levels of care in the Autonomous Community of Catalonia (Spain): primary care, hospitals, hospital and home palliative care (PC), and medium-long stay units. The development cohort included 24 healthcare centres (16 primary care, 3 hospitals, 3 home palliative care teams, and 2 medium-long stay centres). The validation cohort included 7 healthcare centres (1 primary care, 2 hospitals, 3 home PC teams, and 1 medium-long stay centre).

The results from the development and validation cohorts, along with a secondary analysis of the prevalence of ethical issues based solely on the development cohort, were published in 2018, 2023, and 2021, respectively [9-11,13]. Current study presents a secondary analysis of the prevalence of ethical issues using pooled data from both cohorts. The objectives are to increase sample size and consistency, compare results between the two cohorts, and analyze their evolution during follow-up (Figure 1).

### *2.2. PALCOM Scale of Palliative Complexity*

The PALCOM scale is a predictive tool for assessing complexity of palliative care needs, consisting of five multidimensional domains: (a) symptomatic burden; (b) refractory pain; (c) functional decline; (d) socio-family risk factors; and (e) ethical issues (Table 1). Each domain is scored dichotomously, with 0 indicating absence and 1 indicating the presence of the corresponding variables [9-11]. The final score is the sum of the values across all domains. Patients scoring 4-5 are classified as high complexity and require systematic, intensive intervention by multidisciplinary palliative care (PC) teams, whether shared with referring teams or not. Those scoring 2-3 are classified as medium complexity and need systematic intervention by multidisciplinary PC teams, at an intensity adjusted to their needs, whether shared with referring teams or not. Patients scoring 0-1 are

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classified as low complexity and generally do not require systematic intervention by multidisciplinary PC teams, except for occasional consultations.

### 2.3. Definition of ethical issues

The identification of ethical issues can depend on the individual interpretation of observers. Therefore, the research team agreed on the following operational definition for both cohorts: a discrepancy in shared decision-making in a specific situation where it is necessary to choose between opposing options, morally or existentially acceptable from the individual perspective of the different participants in the deliberation. The observed ethical issues were classified according to the sub-categories identified in the analysis of the fifth domain of the PALCOM scale in the development cohort [9]: **a)** Related to information; b) Related to the proportionality of therapeutic and supportive measures (discrepancies in proportionality among family members, between the patient/family and the care team, and among care team members); c) Related to research and clinical trials; d) Related to palliative sedation; e) Related to the desire to hasten death; f) Other unspecified issues.

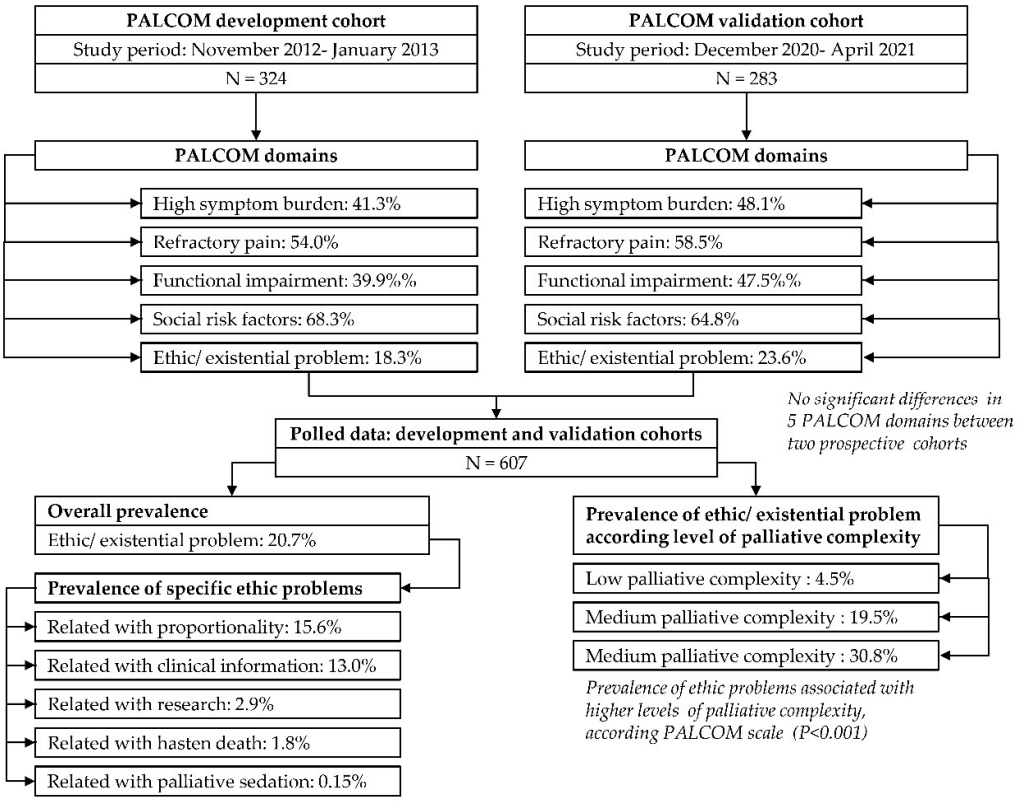


**Figure 1.** Flow-Diagram of Pooled Data from PALCOM Cohorts: Prevalence of Ethical Issues in Advanced Cancer Patients.

### 2.4. Objectives

The main objective of this study was to determine the overall prevalence of ethical issues in patients with advanced cancer. The secondary objectives were: a) to identify the prevalence of different sub-categories of ethical issues; b) to compare the prevalence between the two cohorts and assess their consistency; c) to describe the evolution of these issues over the 6-month follow-up period of the study.

### 2.5. Inclusion criteria

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We proposed to consecutively include in the study all patients who met the following inclusion criteria: age ≥ 18 years, diagnosis of advanced cancer, clinically estimated life expectancy ≤ 6 months, and signed informed consent.

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**Table 1.** PALCOM scale of complexity of palliative care needs for advanced cancer patients.

*Would you be surprised if the patient died in the next 12 months? If the answer is no, the PALCOM instrument can determine the complexity allows managing the intervention of specialized Palliative Care teams.*

**1. Is a high symptom burden detected?**

Presence of ≥5 chronic symptoms with at least a moderate intensity (Visual Analogue Scale or Numeric Ratting Scale ≥4/10) out of 10 systematic

- Pain
- Weakness
- Constipation
- Insomnia
- Anxiety
- Anorexia
- Nausea-vomiting
- Dyspnoea or cough
- Drowsiness
- Sadness

**2. Are there any markers of difficult pain control?**

Any of the following characteristics can lead to potentially difficult pain:

- Neuropathic pain.
- Mixed pain (nociceptive and neuropathic)
- Breakthrou
- Pain associated with a history of addiction to alcohol or other substances of abuse.
- Pain associated with cognitive impairment.
- Pain assoc distress.

**3. Is there functional impairment?**

Person who requires relevant assistance for activities of daily living. (E.g. Barthel index ≤60 or Karnofsky index ≤50-60%)

**4. Any socio-familial risk factors?**

- Absence of identified caregiver.
- Caregiver limitations due to advanced age, health problems, or socio-family or economic burdens.
- Minors or more than one member of the nuclear family who needs support.
- Risk of severe family burnout.
- Other com vulnerabil addiction

**1. Any ethical or existential conflict?**

- Conflicts related to information (denial, conspiracy silence, ...)
- Disagreement between patient/family and healthcare team.
- Desire to euthanasi
- Healthcare team disagreement.
- Loss of meaning in life or existential distress.
- Spiritual distress.
- Others...

Each of these 5 domains is scored dichotomously, 0 absence or 1 presence of any of the variables, the sum, total score of the PALCOM scale.

- **Low complexity (0-1):** Basic palliative care is recommended. Referring team to get back in contact if patient becomes more com consultation with specialist palliative care may be needed for a comprehensive assessment or management of difficult isolated
- **Medium complexity (2-3):** Specialised palliative care is systematically recommended (hospital teams, home support teams or
- **High complexity (4-5):** Intensive specialised palliative care is systematically recommended (teams in the hospital, support tea care services).

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*2.6. Main outcome variable*

The main variable in this study was the prevalence of ethical issues in patients with end-of-life cancer at the baseline visit. The prevalence of ethical issues was evaluated both globally and broken down into the aforementioned sub-categories (information, proportionality, research, palliative sedation, miscellaneous) at the baseline visit and monthly during follow-up.

*2.7. Descriptive variables*

The following descriptive and clinical variables were recorded and analyzed: age, gender, primary origin of the cancer, survival, place of death, level of palliative care complexity, and domains of the PALCOM scale: a) high symptom burden (≥5 symptoms of at least moderate intensity, in a systematic record of 10 symptoms based on the Edmonton Symptom Assessment Scale model [24]); b) potentially refractory pain, according to the Edmonton Classification System for Cancer Pain [25-27]; c) Karnofsky Performance Status; d) socio-familial risk factors.

*2.8. Data collection, sample size and statistical analysis*

All study variables were recorded directly by the treating professional in an electronic data collection notebook, coded to ensure the confidentiality of participants' personal data. No individuals outside the research project had access to the coded database.

In both cohorts, the sample size estimation was based on previous studies and the maximum recruitment capacity of the participating centres, considering that the variables had to be recorded under the conditions of their daily clinical practice. The prevalence of patients presenting ethical issues and the frequencies of sub-categories were evaluated both generally and stratified by the level of complexity of the PALCOM scale and by month of follow-up. The prevalence observed in the development and validation cohorts were compared, considering that they were conducted at different times and by different care teams. Categorical or dichotomous variables were analyzed using absolute and relative frequencies. Continuous variables were described by calculating the mean value and standard deviation (SD) with a 95% confidence interval. For the comparison of variables according to complexity levels, Fisher's exact test and the non-parametric Mann-Whitney-Wilcoxon test were used.

## 3. Results

A total of 607 patients were included in the pooled analysis, with 324 (53.4%) from the development cohort and 283 (46.6%) from the validation cohort. Monthly follow-up data were available only for the validation cohort, as this variable was not recorded in the development cohort.

In the pooled data, the mean age of the patients was 70 years (SD ±11), and 350 were men (57.7%). Three hundred fifty-five patients were included in the hospital (58.5%), and 255 (41.5%) in community health centres. The most common primary cancer origins were lung (23.1%), followed by colon (15.5%), prostate (7.6%), and breast (6.8%). Five hundred patients had metastatic disease (82.4%), and 107 had advanced loco-regional disease (17.6%). At the time of inclusion, 462 (76.1%) patients were undergoing cancer treatment. The most frequent symptoms were asthenia (93.6%), pain (80.7%), anorexia (78.9%), anxiety (69.5%), sadness (69.4%), and insomnia (60.6%). The frequencies of the five domains of the PALCOM scale were: a) high symptom burden 44.5%; b) potentially refractory pain 56.2%; c) Karnofsky Performance Status ≤60% 43.5%; d) socio-familial risk factors 66.7%; e) ethical issues 23.4%. Three hundred seventy-nine patients (62.4%) died before the end of the maximum follow-up period of 6 months. No significant differences were observed between the two cohorts in terms of symptom frequencies or the domains of the PALCOM scale (Tables 2 and 3).

*3.1. Prevalence of Ethical Issues*

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In the pooled data, 126 patients (20.7%) presented at least one ethical issue (59 from the development cohort and 67 from the validation cohort) (Table 4). A total of 204 ethical issues were recorded (117 in the development cohort and 87 in the validation cohort). Therefore, the average number of ethical issues per patient was 1.6 (1.9 in the development cohort and 1.3 in the validation cohort). No significant differences were observed between the two cohorts.

In the pooled data, 79 patients (13.0%) presented issues related to information. This was slightly more frequent in the development cohort (15.7%) than in the validation cohort (10.0%), but the difference was not statistically significant. In the pooled data, 95 patients (15.6%) presented issues related to the proportionality of therapeutic or supportive measures, with no significant differences between the development cohort (16.7%) and the validation cohort (14.5%). The discrepancies in proportionality were: a) among different family members in 47 patients (7.7%); b) between the patient or their family and the healthcare team in 27 patients (4.4%); c) among different members of the healthcare team in 25 patients (4.1%). No significant differences were observed between the frequencies in the development and validation cohorts. In the pooled data, 18 patients (2.9%) presented issues related to research, with no significant differences between the development cohort (2.5%) and the validation cohort (3.5%). In the pooled data, 11 patients (1.8%) explicitly, consistently, and repeatedly expressed the desire to hasten death, with no significant differences between the development cohort (1.2%) and the validation cohort (2.4%).

### *3.2. Evolution During Follow-Up*

The monthly probability of presenting ethical issues during the 6-month follow-up was evaluable only in the validation cohort. A total of 67 patients (23.7%) presented ethical issues at the baseline visit. Among the patients who were alive in the first month of follow-up, 44 (17.1%) presented ethical issues, 32 (15.9%) in the second month, 25 (15.9%) in the third month, 18 (14.1%) in the fourth month, 18 (15.8%) in the fifth month, and 14 (14.4%) in the sixth month (Figure 2). The probability of presenting ethical issues was significantly higher at the baseline visit ($p<0.001$), with no significant differences in this monthly probability from the first month of follow-up onwards.

**Table 2.** Characteristics of patients according to the development and validation cohorts of the PALCOM scale and pooled data.

| | | Development cohort N (%) | Validation cohort N (%) | p | PALCOM pooled data N (%) |
|---|---|---|---|---|---|
| Total | | 324 | 283 | | 607 |
| Gender | Male | 189 (58.0) | 161 (56.9) | 0.280 | 350 (57.7) |
| Age | (mean ±SD*) | 69 (SD±59-80) | 71 (SD±59-81) | 0.320 | 70 SD±59-80 |
| *Primary origin* | | | | | |
| | Lung | 71 (21.9) | 64 (24.4) | 0.310 | 140 (23.1) |
| | Colon | 38 (11.7) | 56 (19.8) | 0.290 | 94 (15.5) |
| | Pancreas | 28 (8.6) | 18 (6.4) | 0.270 | 46 (7.6) |
| | Breast | 22 (6.8) | 19 (6.7) | 0.190 | 41 (6.8) |
| | Prostate | 18 (5.5) | 28 (9.9) | 0.210 | 46 (7.6) |
| | Others | 146 (45.1) | 93 (32.8) | 0.300 | 239 (39.4) |
| *Symptom prevalence* | | | | | |
| | Asthenia | 299 (92.2) | 269 (95.1) | 0.210 | 568 (93.6) |
| | Anorexia | 253 (78.1) | 226 (79.9) | 0.079 | 479 (78.9) |
| | Pain | 245 (75.6) | 245 (86.6) | 0.100 | 490 (80.7) |
| | Nausea | 110 (34.0) | 68 (24.0) | 0.080 | 178 (29.3) |
| | Constipation | 202 (62.3) | 162 (57.2) | 0.110 | 364 (59.9) |
| | Dyspnoea | 149 (45.9) | 111 (39.2) | 0.220 | 260 (42.8) |
| | Insomnia | 191 (58.9) | 177 (62.5) | 0.180 | 368 (60.6) |
| | Anxiety | 238 (73.4) | 184 (65.0) | 0.090 | 422 (69.5) |

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| | | | | |
|---|---|---|---|---|
| Sadness | 225 (69.4) | 196 (69.3) | 0.220 | 421 (69.4) |
| *PALCOM domains* | | | | |
| High symptom burden | 134 (41.3) | 136 (48.1) | 0.190 | 270 (44.5) |
| Refractory pain | 175 (54.0) | 166 (58.5) | 0.220 | 341 (56.2) |
| Karnofsky index ≤60% | 129 (39.9) | 135 (47.5) | 0.210 | 264 (43.5) |
| Socio-familial risk | 221 (68.3) | 184 (64.8) | 0.420 | 405 (66.7) |
| Ethical issues | 59 (18.3) | 67 (23.6) | 0.080 | 126 (20.7) |

**Table 3.** PALCOM scale domains according to the level of complexity of palliative care needs.

| | **Development cohort** | | | | **Validation cohort** | | | | **Pooled data** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| N (%) | 324 (53.4% of polled data) | | | | 283 (46.6% of polled data) | | | | 607 | | | |
| Hospital inclusion | 180 (55.6) | | | | 175 (61.8) | | | | 355 (58.5) | | | |
| Community inclusion | 144 (44.4) | | | | 108 (38.2) | | | | 252 (41.5) | | | |
| | Low | Medium | High | | Low | Medium | High | | Low | Medium | High | |
| | 51 (15.8) | 139 (43.0) | 133 (41.2) | | 67 (23.7) | 167 (59.9) | 49 (17.3) | | 118 (19.5) | 306 (50.5) | 182 (30.0) | |
| PALCOM domains | | | | p | | | | p | | | | p |
| High symptom burden | 20 (39.2) | 99 (71.2) | 115 (86.5) | <0.001 | 6 (8.9) | 83 (49.7) | 47 (95.5) | <0.001 | 26 (22.0) | 182 (59.4) | 162 (89.0) | <0.001 |
| Refractory pain | 13 (25.5) | 69 (49.6) | 93 (69.9) | <0.001 | 30 (45.7) | 93 (55.4) | 43 (87.8) | <0.001 | 43 (36.4) | 162 (52.9) | 136 (74.7) | <0.001 |
| Karnofsky index ≤60% | 17 (33.3) | 53 (38.1) | 59 (44.4) | <0.001 | 4 (5.9) | 90 (53.6) | 41 (83.7) | <0.001 | 21 (17.8) | 143 (46.7) | 100 (54.9) | <0.001 |
| Socio-familial risk | 33 (64.7) | 81 (58.3) | 107 (80.5) | 0.055 | 13 (19.4) | 126 (75.0) | 45 (91.8) | <0.001 | 46 (42.5) | 207 (67.6) | 152 (83.5) | <0.001 |
| Ethical issues | 1 (2.0) | 25 (18.0) | 33 (24.8) | <0.001 | 4 (5.9) | 34 (20.2) | 29 (59.2) | <0.001 | 5 (4.2) | 59 (19.5) | 56 (30.8) | <0.001 |
| Death within 6 months | 18 (35.3) | 77 (55.4) | 99 (74.3) | <0.001 | 33 (49.2) | 114 (68.3) | 38 (77.6) | <0.001 | 51 (43.2) | 190 (62.7) | 138 (75.8) | <0.001 |
| Hospital death | 3 (5.9) | 24 (17.3) | 40 (30.1) | <0.001 | 6 (8.9) | 25 (22.1) | 12 (30.8) | <0.001 | 9 (7.6) | 49 (16.0) | 52 (28.6) | <0.001 |

**Table 4.** Frequency of specific ethical issues.

| | | PALCOM development n (%) | PALCOM validation n (%) | p | Pooled data |
|---|---|---|---|---|---|
| | Total | 324 (53.4) | 283 (46.6) | - | 607 |
| | N patients with ≥1 ethical issue | 59 (18.3) | 67 (23.7) | 0.419 | 126 (20.7) |
| | Specific ethical issues | | | | |
| - | Information | 51 (15.7) | 28 (10.0) | 0.071 | 79 (13.0) |
| - | Proportionality of therapeutic or support measures | 54 (16.7) | 41 (14.5) | 0.580 | 95 (15.6) |
| * | Discrepancies within family members | 26 (8.0) | 21 (7.4) | 0.879 | 47 (7.7) |
| * | Discrepancies between the care team and patient or family | 14 (4,3) | 13 (4.6) | 0.890 | 27 (4.4) |
| * | Discrepancies within the care team | 12 (3.7) | 13 (4.6) | 0.684 | 25 (4.1) |
| * | Discrepancies respect to withdrawal life support | 2 (0.6) | 1 (0.3) | 0.900 | 3 (0.5) |
| - | Research and clinical trials | 8 (2.5) | 10 (3.5) | 0.482 | 18 (2.9) |
| - | Request to hasten death | 4 (1.2) | 7 (2,4) | 0.363 | 11 (1.8) |
| - | Conflicts associated with palliative sedation | 0 | 1 (0.3) | 0.257 | 1 (0,15) |
| | Total ethical issues | 117 | 87 | 0.202 | 204 |

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| | | | | |
|---|---|---|---|---|
| Ethical issues/patient | 1.9 | 1.3 | 0.202 | 1.6 |

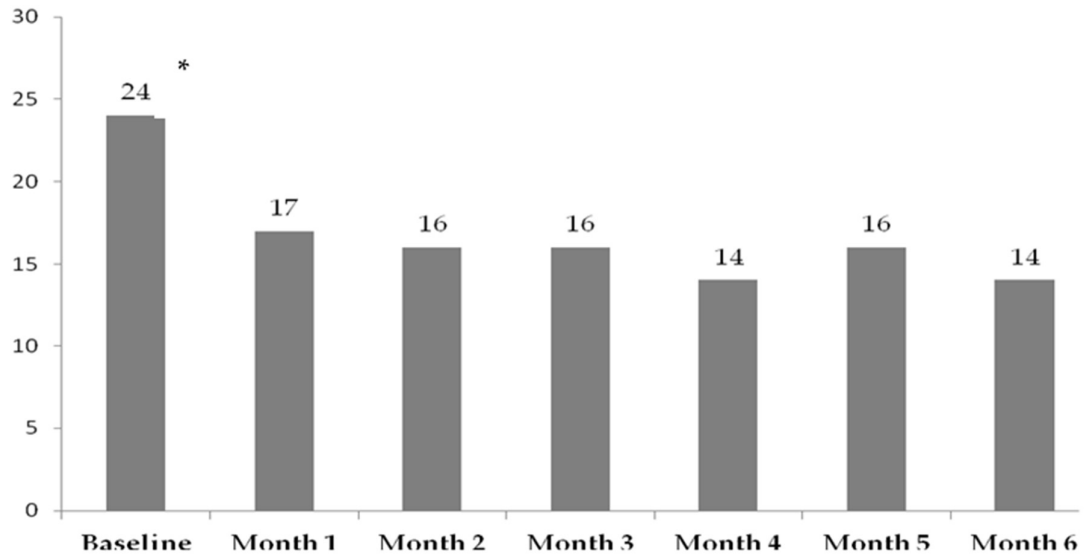


**Figure 2.** Overall frequencies of ethical issues during follow-up in validation cohort (%).* The prevalence of ethical issues at baseline was significantly higher than that observed in the subsequent follow-up months ($p<0.001$).

*3.3. Prevalence of Ethical Issues According to Palliative Complexity Level on the PALCOM Scale*

The level of palliative complexity according to the PALCOM scale depends on the interaction of five assessment domains: symptom burden, potentially refractory pain, functional impairment, socio-familial risk, and ethical issues. The presence of 4-5 affected domains corresponds to high complexity cases, 2-3 to medium complexity, and 0-1 to low complexity.

In the aggregated data, 118 patients (19.5%) were classified as having low palliative complexity, 306 (50.5%) as medium, and 182 (30.0%) as high. Higher complexity levels are significantly associated with increased six-month mortality (low 43.2%, medium 62.7%, high 75.8%) ($p<0.001$) and a higher probability of in-hospital death (low 7.6%, medium 16.0%, high 28.6%) ($p<0.001$). The likelihood of presenting ethical issues, both in the aggregated data and when broken down between the two cohorts, is significantly higher at greater levels of palliative complexity according to the PALCOM scale ($p<0.001$): low 4.2%; medium 19.5%; and high 30.8% (Table 3).

## Discussion

We believe that the analysis of pooled data from the development and validation cohorts of the PALCOM scale is appropriate to expand the study sample and improve the consistency of the preliminary results published regarding the prevalence of ethical issues, which were initially based solely on the development cohort. The absence of significant differences in socio-demographic characteristics, the frequency of the five domains of the PALCOM scale, the identified levels of palliative complexity, and six-month mortality between both cohorts confirms the consistency of their combined analysis.

*4.1. Overall Prevalence of Ethical Issues*

In the polled data, 21% of patients presented at least one ethical issue according to the treating professionals. It is noteworthy that many of these patients simultaneously presented multiple ethical issues (an average of 1.6 ethical issues per patient). It is clear that ethical issues can cause significant

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discomfort for all parties involved in their discussion. The first step in addressing such a problem is its identification, and the second is to manage the conflict explicitly and respectfully. Conflict management skills can be essential for health professionals in resolving these issues. In fact, it is noteworthy that the prevalence of ethical issues in this study was significantly higher at the baseline visit compared to the prevalence observed during the subsequent six months of follow-up. These data suggest that early identification and intervention can reduce the frequency of ethical issues and, therefore, improve the outcomes of patient support measures. Overall, we consider these findings to be novel and relevant due to the high observed prevalence and the lack of previously published data in this area.

### *1.1. Prevalence of Different Categories of Ethical Issues*

In this study, ethical issues were classified into five different categories: information, proportionality, research, palliative sedation, and the desire to hasten death. This classification was agreed upon by the research team of the development and validation cohorts of the PALCOM scale. It was based on multiple expert opinion publications that described the theoretical aspects of the issues or surveys that identified the main ethical concerns of healthcare professionals in the end-of-life process [15-23]. Interestingly, all 214 ethical issues detected in the aggregated data of this study could be included in one of these predetermined categories.

#### 4.1.1. Ethical issues related to information

Communication between doctor and patient is a process of information exchange aimed at providing the patient with the necessary knowledge to make reflective and autonomous decisions in a specific clinical context. It is an asymmetric and bidirectional process. The healthcare professional, who has knowledge of the clinical data, must explain and advise the patient clearly, truthfully, comprehensibly, and personally about everything concerning their health, and must recognize the value and meaning the patient attributes to the received information [28-30]. Available literature confirms that adequate communication can improve adherence to proposed treatments, quality of life, and patient satisfaction, as well as reduce uncertainty and emotional impact [31-45].

In the complex process of informing about the diagnosis, extent, treatment options, and prognosis of cancer, ethical issues may arise. These issues are related to both the quality and quantity of the information provided, which is often modulated according to the professional's criteria in response to the patient's or family's reaction, as well as the timing and context in which the information is offered. The healthcare professional must manage multiple and unpredictable coping styles to the life-threatening nature of the disease, where the patient's expectations and hopes are not always realistic, and where there may be tendencies towards compassionate limitation of information by the family.

In this study, 13% of patients presented one of the following decision-making problems related to information: a) information exceeding the patient's desired limits; b) adaptive denial; c) conspiracy of silence. Information exceeding the patient's desired limits was described as that which caused a high emotional impact and hindered their participation in decision-making because it was provided rapidly in all its aspects, without respecting the patient's opinion on the amount, timing, or context in which it was given. Denial was described as an adaptive process in which the patient, implicitly or explicitly, preferred not to know all aspects of their disease, especially the prognosis, or adopted alternative arguments to avoid recognizing a reality they felt was unmanageable. The conspiracy of silence was defined as the explicit agreement of the family to avoid providing information, especially the prognosis, with a compassionate intention based on the belief that the patient does not have sufficient emotional resources to face the life-threatening situation.

Various studies indicate that between 20% and 69% of patients with advanced and incurable cancer are unaware of both the prognosis and the palliative intent of chemotherapy or radiotherapy treatment [40,46-50]. Communication with the patient is an ethical and clinical imperative for all

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healthcare professionals. If a patient has insufficient information, it is the healthcare professional's duty to expand it truthfully, comprehensibly, and personally to ensure autonomy in decision-making. In this study, the prevalence of ethical issues related to information was limited to situations where the previously provided information or the adaptive reaction to it generated an ethical issue that hindered shared decision-making with the patient. This is likely the reason for the observed differences between the general record on the lack of knowledge about the disease prognosis mentioned earlier (20-69%) and the data provided by this study (13%).

In 2018, the healthcare ethics consultation service at Memorial Sloan Kettering Cancer Center in New York published a retrospective study on the prevalence of ethical issues consulted. According to this study, 8% of these consultations were related to communication problems and 13% to cases of denial by the patient or their family [51].

#### 4.2.2. Ethical issues related to proportionality

Deliberation on the proportionality of healthcare interventions caused an ethical issue in 16% of the cases included in this study. The observed issues focused on two distinct situations: futility and treatment refusal. Futility is defined as a medical act considered useless or disproportionate due to its unlikely efficacy and lack of reasonable benefit in an individual clinical condition, according to available scientific evidence [52-53]. Refusal of treatment that healthcare professionals consider appropriate requires careful deliberation but is not ethically disputable if it is based on the patient's reflective reasoning and the conditions of their autonomy of will are met (cognitive competence, complete information, and absence of external interferences) [54-56].

In this study, most discrepancies regarding proportionality were observed among the patient's family members (8%). Less frequently, proportionality conflicts were recorded between the patient/family and the healthcare team (4%) or among the different healthcare professionals involved in the patient's care (4%). Discrepancies regarding the withdrawal of life support were observed in very few cases (0.5%).

In the previously mentioned study by the Memorial Sloan Kettering Cancer Center in New York, 22% of the consultations to the healthcare ethics service were related to the futility of healthcare interventions, 5% to treatment refusal, and 2% to the withdrawal of life support. Additionally, they observed that in 11% of these consultations, there were discrepancies among the patient's family members, in 3% between the patient/family and the healthcare team, and in 5% among the members of the treating team [51].

#### 4.2.3. Ethical Issues Related to Research

Research in patients with advanced cancer who have not responded to conventional treatments undeniably represents an ethical challenge. The vulnerability of these patients and the desperate need to find therapies that delay the progression of their disease can lead to misinterpretation of information, affect the informed consent process, and encourage acceptance of inclusion in an early-phase clinical trial [57-61].

In this study, ethical issues related to research were detected in 3% of the included patients. As expected, all patients participating in clinical trials received verbal and written information and signed an informed consent form. However, researchers identified that some of these patients' expectations were not fully aligned with the actual expected outcomes, or they accepted inclusion in the trial out of fear of being abandoned by the healthcare system. It is noteworthy that conflicts related to research represented 2% of the consultations to the healthcare ethics service at Memorial Sloan Kettering Cancer Center in New York [51].

#### 4.2.4. Ethical issues related to palliative sedation

Palliative sedation is defined as the deliberate administration of sedatives in the necessary doses and combinations to reduce the level of consciousness of a terminal patient for the time required to

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adequately relieve one or more refractory symptoms [62-64]. Approximately 25% (10-50%) of patients with advanced cancer require palliative sedation in the final days of life [64].

Both the ethical aspects and procedures for the application of terminal sedation, as well as the differential criteria with euthanasia, are widely accepted. However, in daily clinical practice, dilemmas can occasionally arise related to the interpretation of the ethical requirements of palliative sedation: a) definition of refractory symptoms; b) adequacy of sedative doses proportional to the goal of reducing the level of consciousness, not shortening life span; c) involvement of the patient or their family in the sedation decision (explicit, implicit, or delegated consent).

Currently, ethical issues related to palliative sedation are infrequent. In fact, in this study, only one case was detected where the decision for palliative sedation was ethically complex (0.15%). In 2016, a study based on a survey of professionals was published to determine the frequency and difficulty of resolving 20 previously agreed-upon ethical dilemmas in the end-of-life process. The analysis of the responses concluded that the frequency and difficulty of ethical issues related to palliative sedation were low, ranking 18th among the 20 ethical dilemmas examined [16]. In the study by the healthcare ethics service at Memorial Sloan Kettering Cancer Center in New York, no consultations related to palliative sedation were recorded [51].

#### 4.2.5. Ethical issues related to the desire to hasten death

In the context of incurable cancer, some patients may wish to end their lives. The desire to hasten death is a complex phenomenon influenced by various dimensions of human suffering (physical, emotional, social, spiritual) [65-69]. In some cases, intolerable and refractory physical or psychological suffering may be the determining factor. In others, it may be physical dependency, unwanted loneliness, lack of social support, or the feeling of being a burden to others. It can also appear in patients who have serenely accepted death and consider the remaining time to live as useless and painful.

In this study, the desire to hasten death was recorded as the idea of not wanting to continue living in conditions that the patient considered intolerable and that violated their concept of personal dignity, argued reflectively and repeatedly. Therefore, patients who occasionally expressed the desire to die in the context of a specific crisis of physical or psychological suffering, or those who expressed it as a symptom of major depression, were not included. Identification was carried out in the context of the study's systematic multidimensional evaluation, according to the clinical judgment of the treating professional, without using any instrument specifically designed to detect the desire to hasten death.

The prevalence of the desire to hasten death in this study was 1.8%. The available literature on the prevalence of the desire to hasten death is very heterogeneous, ranging from 1.5% to 35%, depending on the detection instrument used, the agreed cutoff point, and the care setting [67-69].

In recent years, euthanasia has been a topic of social debate in many developed countries. The core of the discussion is whether a person suffering from an incurable and progressive disease that causes intolerable and refractory physical or psychological suffering can decide when, how, and where to die. It is a discussion that seeks to harmonize the right to life and the right to freedom and dignity from a pluralistic and possibilistic perspective. Seven countries worldwide have approved laws regulating euthanasia [70]. In Spain, where this study was conducted, euthanasia was legalized in March 2021 [71]. It is noteworthy that the study presented was carried out before this law came into effect (June 2021). We do not know if the implementation of this law will influence the free and spontaneous expression of the desire to hasten death.

### *4.1. Ethical aspects and palliative complexity*

Complex systems are defined as those that depend on the interaction of multiple variables in an unstable equilibrium, highly sensitive to changes in initial conditions, with an outcome that is not always predictable [3-8].

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The PALCOM scale identified five domains (symptom burden, refractory pain, functional deterioration, social risk, ethical issues), whose continuous interaction determined the level of complexity of palliative needs in patients with advanced cancer in real clinical practice. Higher complexity levels were associated with high instability (rapid change or death), consumption of PC resources, mortality, and in-hospital death [9-11]. Identifying palliative complexity allows for consistent adjustment of referrals to multidisciplinary PC teams and the intensity of their shared intervention with referring teams.

Ethical issues were identified as a variable with high predictive power for the level of palliative complexity. The data provided by this aggregated analysis confirm that the probability of high palliative complexity is significantly higher in patients presenting ethical issues.

### *4.1. Study limitations*

The PALCOM scale, the source of the data for this study, was designed for adult patients with advanced cancer. Therefore, the results are not generalizable to patients with non-oncological chronic diseases or to the pediatric population.

This study was conducted within a public healthcare system with universal access for all citizens, which includes palliative care in its service portfolio. We do not know if the observed data are generalizable to different healthcare settings.

The data provided correspond to two prospective cohorts of patients with advanced cancer, conducted with the same inclusion and evaluation system by different teams at different times. We believe that the absence of statistically significant differences between socio-demographic and outcome variables in the comparison of both cohorts confirm the consistency of the aggregated analysis and the absence of inclusion or evaluation biases.

## Conclussions

This study confirms that ethical issues are highly prevalent in the end-of-life process of patients with advanced cancer. Ethical issues related to information and proportionality in the shared decision-making process are the most frequent. The presence of ethical dilemmas directly influences the complexity of palliative care needs. Early identification and addressing of ethical issues reduce their frequency during patient follow-up. Most observed ethical issues are directly or indirectly associated with patient autonomy.

### *Practical Implications*

The data provided by this study confirm that, in routine clinical practice, it is essential to systematically explore the individual value and meaning each patient attributes to their illness and to identify emerging ethical conflicts. Early identification and addressing of these issues can improve the outcomes of supportive care. In this context, communication skills and basic training in bioethics play a crucial role for all healthcare professionals attending to incurable and life-threatening conditions.

### *Implications for Research*

Due to the high prevalence of ethical issues in the end-of-life process of patients with advanced cancer and their impact on palliative complexity in real clinical practice, we believe it would be interesting to design prospective studies specifically aimed at analyzing the prevalence of different ethical issues and the determining factors for their occurrence.

We do not know the impact of euthanasia regulation laws on the prevalence of patients expressing a consistent desire to hasten death. An update of the PALCOM study would allow us to determine if there are differences in the prevalence of the desire to hasten death between a period before and after the implementation of the euthanasia regulation law in our country.

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**Informed Consent Statement:** All patients received prior written information about the study. Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The data can be shared upon request.

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