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Defining the Core Constituent Elements of the Early Palliative Care Intervention:

A Prospective Qualitative AI Analysis of Its Delivery in Real-World Clinical Encounters

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Relatore:
Prof. Leonardo Potenza

Candidata:
Rosa Turina

Correlatore:
Prof. Mario Luppi

Correlatore:
Dott.ssa Marta Lovino

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A Cesare

In questi anni ho imparato tante cose,

ma le più importanti me le avevi già insegnate tu.

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Chapter 1

Introduction

The study in which I participated over the past months focused on early palliative supportive care (ePSC) and its integration into the care pathway of patients with hematological malignancies. The content of palliative care consultations was analyzed directly through transcripts of clinical encounters, using an artificial intelligence (AI) system trained to identify clusters of recurring words and principal thematic areas.

In the future the goal will be to correlate this elements with patient-reported outcomes (PROs) to explore potential associations between the characteristics of clinical communication and patients' quality of life, symptom burden, perceived well-being and end-of-life awareness. This integrated approach aims to enhance understanding of the mechanisms through which early palliative supportive care may influence clinical outcomes and to support the development of increasingly effective and personalized care models. The first introductory chapter provides an **overview of the current state of the art** relevant to these topics.

> *Premise*: it was decided to address the main hematological neoplasms, as they are essential for understanding the thesis project; however, they will be discussed in a concise technical manner, explicitly aimed at explaining the care needs of patients diagnosed with hematological malignancies, and therefore **not** necessarily exhaustive of each individual hematological neoplasm. The focus has been limited to incidence and epidemiology, clinical features, treatment, and prognosis.

1.1 Acute Myeloid Leukemia (AML)

Acute myeloid leukemia (AML) is a malignancy of the stem cell precursors of the myeloid lineage (red blood cells, platelets and white blood cells other than B and T cells). Like other malignancies, it is due to genetic variations that lead to neoplastic and clonal proliferation. It is characterized by defective stem cell hematopoiesis at the bone marrow level, resulting in the accumulation of immature precursor cells at various stages of maturation and a reduced production of healthy, mature blood cells. This latter phenomenon is defined as cytopenia, the main driver of clinical manifestations, such as: anemia (fatigue and dyspnea), neutropenia (increased susceptibility to infections) and thrombocytopenia (increased risk of hemorrhage and bleeding) [1, 3].

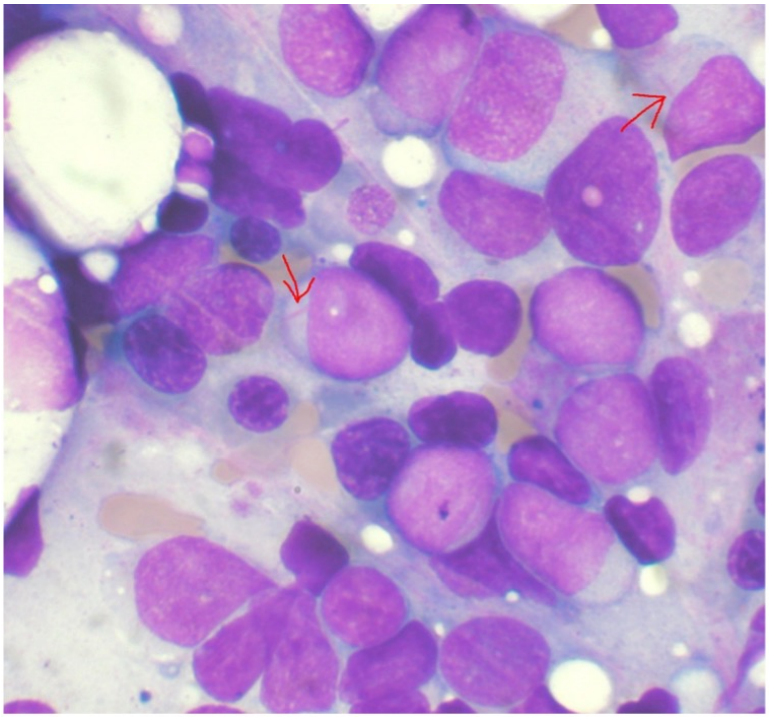

Figure 1.1: Bone marrow aspirate from a patient with acute myeloid leukemia. Arrows indicate a classic histopathological finding known as Auer rods. *Source: Wikipedia* [24].

1.1.1 Incidence and Epidemiology

The incidence of acute myeloid leukemia increases with age, with the risk rising exponentially in patients over 60 years old. The ageing of the European population may therefore be part of the reason for the reported increase in AML incidence in Europe from 3.48 to 5.06 patients per 100 000 individuals over the 37-year period between 1976 and 2013.

The World Health Organization (WHO) in its 2016 updated guidelines distinguishes six groups of AML: (1) AML with recurrent genetic abnormalities, (2) AML with myelodysplasia-related changes, (3) Therapy-related myeloid neoplasms, (4) AML Not Otherwise Specified, (5) Myeloid sarcoma, and (6) Myeloid proliferations related to Down syndrome.

The diagnosis is made by the presence of ≥20% blasts in the peripheral blood or in the bone marrow, or through the presence of unique genetic abnormalities found in the bone marrow regardless of blast count [t(8;21), inv(16), or t(15;17)].

AML is further classified into three prognostic risk groups: **favorable**, **intermediate**, and **adverse**, determined by molecular and cytogenetic abnormalities.

The median age at diagnosis is ~70 years, although, based on the 2016 WHO classification, it has been observed that with advanced age, the relative incidence of AML with recurrent genetic abnormalities **decreases**, while the relative incidence of other AML categories [such as AML with myelodysplasia-related changes (MRC-AML) or therapy-related AML (tAML)] **increases** with age, comprising about 19% and 7% of AML cases, respectively [2, 3].

1.1.2 Treatment

The treatment of AML involves initial induction therapy and post-remission therapy.

Induction Therapy

The goal of induction therapy is to achieve complete remission (CR) with preferably no measurable residual disease (MRD). Choice of initial induction treatment depends on functional status of the patient (performance status and comorbidities), biological status of the disease (best measured by prognostic risk groups: favorable, intermediate and adverse risk disease) and goals of the patient. The two commonly used induction therapies include: (1) cytotoxic chemotherapy with or without targeted therapies and (2) hypomethylating agents with or without targeted therapies.

For all patients with **favorable and intermediate risk AML**, with the goal of cure and who are medically fit enough to tolerate chemotherapy, the backbone of therapy has not changed for 50 years, and is commonly known as 7+3 induction chemotherapy with the addition of various targeted drugs such as a monoclonal anti-CD-33 antibody called Gemtuzumab ozogamicin (GO). FLT3 (FMS-like tyrosine kinase) represents the only mutated protein that can be pharmacologically targeted. If this mutation is present (approximately 30% of AML), agents such as Midostaurin and Lestaurtinib may be administered in combination with conventional chemotherapy.

The upfront cytotoxic treatment consists of a continuous infusion of Cytarabine over 7 days with the addition of an anthracycline (Daunorubicin), given daily for the first 3 days.

For all patients with **adverse risk AML**, however, outcomes with standard 7+3 chemotherapy remain unsatisfactory. Complete remission (CR) rate is only about 40% and median overall survival is in the range of 12–18 months. Even with allogeneic hematopoietic stem cell transplantation, almost half of the patients relapse.

Post-Remission Therapy

The aim of post-remission therapy is to reduce the risk of disease relapse. The main approaches used include further cycles of cytotoxic chemotherapy after remission, such as intermediate or high-dose Cytarabine, with or without the addition of targeted agents, and the allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Supportive Care

Alongside the therapeutic strategy mentioned above, it is essential to highlight that significant advances have been made in **supportive care**, including the widespread availability of high-quality platelet transfusions, improved and less toxic broad-spectrum antibacterial and antiviral therapies, the elimination of post-transfusion hepatitis, and the development of new antifungal agents. Less frequently acknowledged, but equally important, are the benefits of more effective antiemetic regimens, which have substantially reduced complications such as erosive esophagitis and malnutrition, secondary to inadequate oral intake [1, 3].

1.1.3 Survival of AML Patients in Europe

In patients under the age of 65, both prognosis and long-term survival have shown a gradual improvement over time. This positive trend can largely be attributed to advances in supportive care, including more effective prevention and treatment of complications such as severe infections, bleeding events, and treatment-related toxicities. In parallel, there has been greater utilization of allo-HSCT, which remains one of the few potentially curative treatment options for eligible patients.

Nevertheless, despite these therapeutic and management advances, overall survival rates remain disappointingly low. For adult patients diagnosed between 2000 and 2007, the age-standardized 5-year relative survival was approximately 17% (ranging from 16.6% to 17.7%), mainly attributable to the minimal progress attained in AML patients over the age of 65 [2].

In older patients with AML, the presence of comorbidities and a reduced functional status often limits eligibility for intensive chemotherapy (ICT) and, in some cases, may also hinder the administration of lower-intensity therapies (LIT). In

this context, a comprehensive geriatric assessment, encompassing multiple domains such as comorbidity burden, cognitive function, physical performance, and psychological status, is essential prior to treatment initiation [13].

The availability of a new and less toxic formulation, such as CPX-351, of traditional standard ICT (3+7 regimen), as well as lower-intensity therapies (LIT), like the therapeutic association of Azacytidine to Venetoclax (VenAza) and orally administrable agents, such as FMS-like tyrosine kinase 3 (FLT-3) and Isocitrate Dehydrogenase (IDH) inhibitors, and, for LIT-unfit patients, the hypomethylating agent Decitabine and Cedazuridine, have provided significant advancements in this field.

However, while these therapeutic innovations have contributed to improved clinical outcomes, they have also increased the complexity of treatment decision-making in a clinical setting that remains challenging and is often characterized by poor prognosis.

The need for rapid and multifaceted decisions, combined with the urgency of initiating appropriate treatment, introduces **significant uncertainty** and may impose a considerable **emotional burden** on both patients and caregivers.

Furthermore, treatment-related toxicity remains a critical issue, as adverse effects associated with both standard ICT and newer therapeutic approaches can negatively impact patients' quality of life (QoL), exposing them to a broad and variable spectrum of side effects [13].

1.2 Multiple Myeloma (MM)

Multiple myeloma (MM) is a hematologic malignancy defined by the clonal expansion of plasma cells within the bone marrow, leading to excessive production of immunoglobulins. This abnormal protein production contributes to end-organ damage, typically manifesting as **anemia**, **hypercalcemia**, **focal bone lesions**, and/or **renal dysfunction**. Differential diagnosis includes monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), Waldenström Macroglobulinemia (WM), Light-Chain (AL) Amyloidosis, and plasmacytoma.

There is no known etiology of MM, but risk factors are male sex, obesity, occupation (e.g., firefighter), and dioxin and Agent Orange exposure. In newly diagnosed MM, typical findings include anemia (hemoglobin <12), one or more lytic lesions on a conventional radiograph in 79% of cases, elevated creatinine in 19% of cases, lymphadenopathy in 1% of cases, hypercalcemia in 13% of cases, and thrombocytopenia in 5% of cases [4].

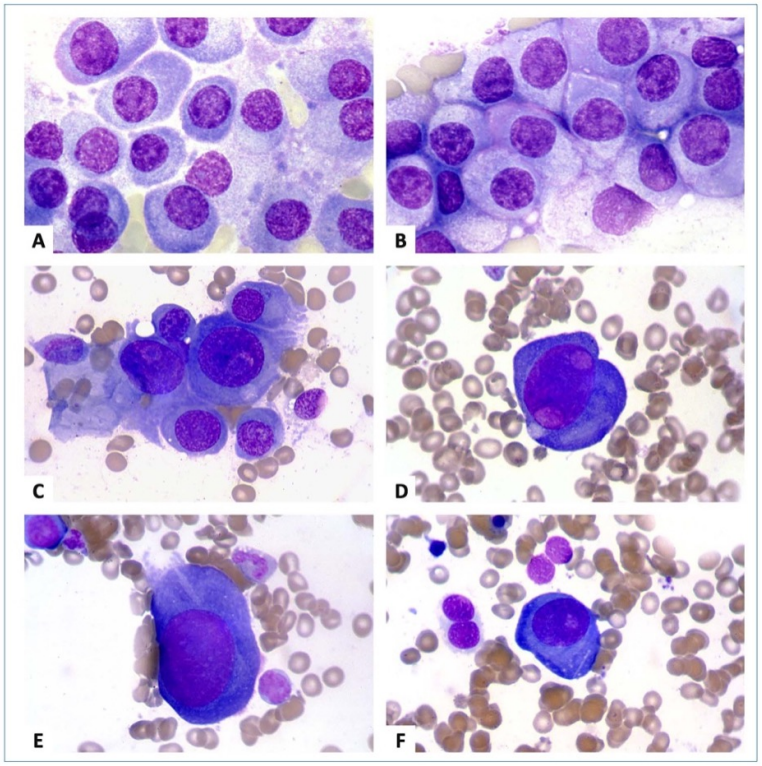

Figure 1.2: Images from the *Haematologica* Atlas of Hematologic Cytology: plasma cell myeloma. *Source: Rosangela Invernizzi* [21].

The Figure (Figure 1.2) shows increased protein in the background with cellular debris (A); plasma cells with reticular cytoplasmic structures and pink-red periphery (center) (B); a group of plasmablasts with irregular cytoplasmic margins, cytoplasmic streamers and crystalline inclusions (C); a giant plasmablast with two macronucleoli and deeply basophilic cytoplasm with immunoglobulin accumulation in the form of amorphous substance or crystals (D). In Figure E and F, note the elongated lance-like and crystalline structures within the cytoplasm of giant plasmablasts [21].

1.2.1 Incidence and Epidemiology

In Europe, multiple myeloma (MM) is the second most common hematological malignancy, with an estimated annual incidence of 4.5–6.0 cases per 100 000 individuals. The disease is most frequently diagnosed in older adults, with a median age at diagnosis of 65–70 years [5].

1.2.2 Treatment

Patients with newly diagnosed multiple myeloma typically receive induction therapy based on combination regimens. These commonly involve at least three agents, such as Lenalidomide (immunomodulator), Dexamethasone, and Bortezomib (cytotoxic), or different regimens depending upon the eligibility of patients for autologous stem cell transplant (ASCT). The primary aim of this initial treatment phase is to achieve maximal tumor burden reduction while optimizing conditions for effective stem cell collection.

After induction chemotherapy, patients are administered high-dose Melphalan, followed by ASCT and consolidation and/or maintenance/extended therapy [4].

For the treatment of **transplant-ineligible** patients with newly diagnosed MM (NDMM), DaraRd, DaraVM plus prednisone and VRd are the standard of care regimens recommended by the EHA [5].

Supportive Care

Patients with multiple myeloma may develop a wide range of clinical complications throughout the natural history of the disease and during the course of therapeutic interventions. The integration of comprehensive supportive care is therefore essential to optimize both quality of life and overall survival.

- **Osteolytic bone disease** is the most common complication in patients with MM, leading to deterioration of quality of life and patient outcomes. A phase III trial has compared the antiresorptive agents denosumab and zoledronic acid in 1,718 patients receiving treatment for NDMM with at least one bone lesion.
- **Anemia**, mainly caused by the mechanisms underlying anemia in chronic disease, for which excellent results have been achieved by erythropoiesis-stimulating agents.
- **Infections**, which are the main cause of death in patients with myeloma, due to T cell immune dysfunction and changes in the B cell compartment. Studies have shown a reduced occurrence of febrile episodes and death with the addition of prophylactic Levofloxacin to active treatment for NDMM during the first 12 weeks.
- **Renal impairment**, present in up to 20% of patients at diagnosis; Lenalidomide dose reduction is required due to its renal clearance [5].

1.2.3 Survival of MM Patients in Europe

Over the past two decades, survival outcomes have improved markedly, particularly among patients enrolled in clinical trials: approximately 60% of those eligible for ASCT were still alive 10 years after the procedure.

Despite these advances, real-world data remain less encouraging. According to the Surveillance, Epidemiology, and End Results (SEER) Program, the overall 5-year survival rate for MM was 61.1% in 2024, and only 10–15% of patients achieve a life expectancy comparable to that of the general population. Moreover, most patients ultimately experience drug resistance and disease relapse, which often progresses to forms that are refractory to currently available treatments [5, 6].

1.3 Lymphoma (LYM)

Lymphomas represent a heterogeneous group of malignant neoplasms originating from cells of the lymphatic system, primarily involving lymphoid tissues. They are traditionally classified into two major categories: **Hodgkin lymphoma (HL)** and **non-Hodgkin lymphomas (NHLs)**. While HL is characterized by the presence of Reed–Sternberg cells and relatively homogeneous biological behavior, NHLs comprise a diverse and complex group of entities with distinct morphological, immunophenotypic, genetic, and clinical features. Among these, specific subtypes such as **Burkitt lymphoma (BL)** represent highly aggressive forms, whereas other NHL subtypes exhibit a wide range of clinical courses, from indolent to rapidly progressive disease.

The pathogenesis of lymphoma is complex and multifactorial, involving the interplay of genetic factors, infections, environmental exposures, and immune status. For instance, HL is strongly associated with infection by the Epstein–Barr virus (EBV), while the high incidence of BL in sub-Saharan Africa has been linked to the concomitant prevalence of EBV infection and malaria. Non-Hodgkin lymphomas (NHLs) are more commonly associated with advanced age, immunosuppressive conditions or therapies, and exposure to chemical carcinogens such as benzene and pesticides.

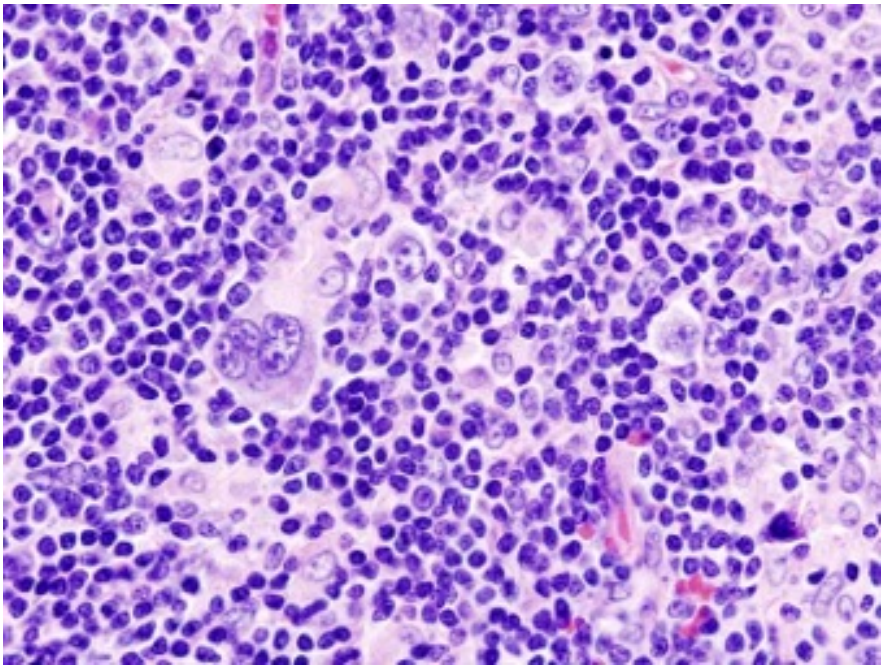

Figure 1.3: Hodgkin disease, with typical giant tumor cells (Reed–Sternberg cells) and an abundant non-neoplastic infiltrate composed mainly of mononuclear leukocytes. *Source: Wikipedia* [23].

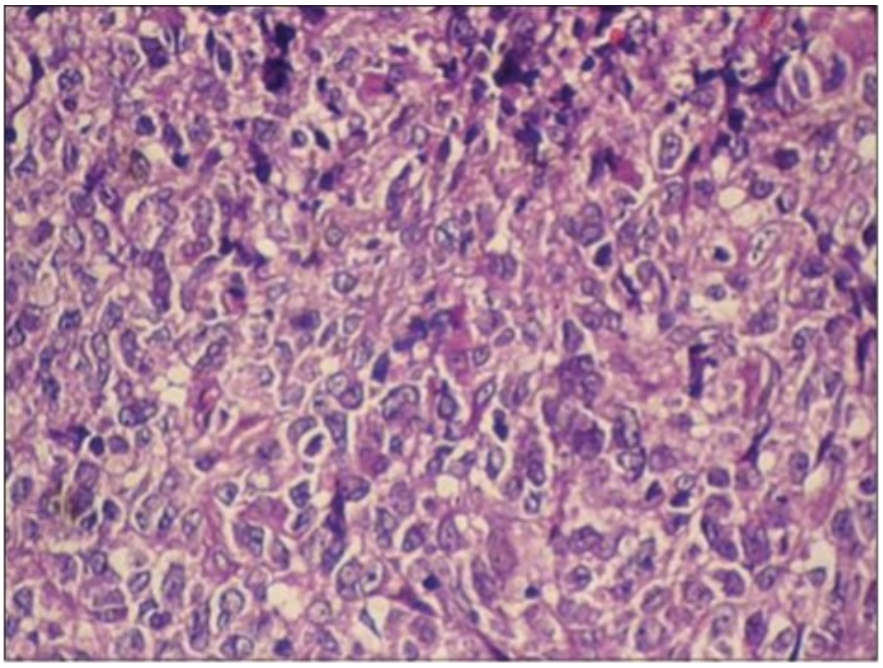

Figure 1.4: Hematoxylin and eosin (40×) section showing sheets of atypical lymphoid cells in a primary non-Hodgkin's lymphoma in extranodal site. *Source: Journal of Oral and Maxillofacial Pathology* [22].

1.3.1 Incidence and Epidemiology

According to Global Cancer Statistics 2020, lymphoma accounts for more than 800 000 new cases and over 500 000 deaths annually, representing a significant part of the global cancer burden.

In recent years, the incidence of NHLs has progressively increased in high-income countries, a trend partly attributable to improvements in diagnostic techniques and to the ageing of the population. In contrast, in regions with a low socio-demographic index, rates of early diagnosis and access to treatment remain substantially lower due to limited healthcare resources, contributing to higher mortality rates.

The incidence of HL and NHL varies significantly by sex and age group. Males generally exhibit higher incidence, morbidity, and mortality:

- HL peaks in the 30–34 age group for both males and females, with males showing higher incidence than females in the 15–59 age range.
- NHL peaks in the 60–65 age group for both sexes; males consistently demonstrate higher incidence than females in all age groups above 50 years.
- BL peaks in the 5–9 and 10–14 age groups in males and females, respectively, and is higher in males than in females during childhood and adolescence [8].

1.3.2 Treatment of Hodgkin Disease

At present, most patients diagnosed with Hodgkin lymphoma can be successfully treated with radiotherapy and/or chemotherapy. Few cancers treated with these modalities have as high a cure rate as Hodgkin's disease.

However, long-term follow-up of cured individuals has demonstrated that the **cumulative toxicity associated with treatment-related complications may approach the mortality attributable to the disease itself.**

Beyond late fatal complications, therapy is also associated with a range of delayed adverse effects, such as: (1) **second malignancies**, like acute myeloid leukemia or the related condition, myelodysplasia; (2) **organ injury**, such as (2.1) **serious infection** with Streptococcus pneumoniae in patients who undergo a splenectomy

as part of the evaluation for treatment of Hodgkin's disease, (2.2) **cardiac and lung disease**, as a consequence of mediastinal radiation, (2.3) **osteonecrosis**, (2.4) **thyroid disease**, (2.5) **gonadal dysfunction**and (2.6) **infertility**in males.

Therefore, future regimens for Hodgkin's disease need to consider both long-term complications of therapy and treatment effectiveness: while a lower cure rate would not be acceptable, reducing late toxicity is an important goal [8].

1.3.3 Treatment of Non-Hodgkin Disease

Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL in the Western Hemisphere. It comprises a heterogeneous group of lymphomas, with different biology and clinical prognoses. R-CHP remains the backbone of therapy, and frontline therapeutic options in fit patients are pola-R-CHP and R-CHOP, whereas elderly or frail/unfit patients may be treated with R-mini-CHOP or palliation. Frontline trials aim to improve outcomes for patients with high-risk disease utilizing R-CHOP combined with novel agents, CAR-T, and bispecific antibodies. Trials in the elderly/unfit population are minimizing and omitting chemotherapy [9].

1.3.4 Survival of Lymphoma Patients in Europe

Despite the high cure rate of HL (5-year survival rate of more than 80%), the heterogeneity and therapeutic complexity of NHL and BL lead to significant prognostic differences, especially in resource-limited areas.

The clinical course of DLBCL tends to be aggressive, with survival typically measured in weeks to months without therapy. Although first-line chemoimmunotherapy may cure most patients, outcomes for patients with relapsed DLBCL are poor. Five-year survival in the US in 2015–2021 was approximately 65%, with poorer 5-year survival of 56% in patients aged 65 and older [8, 9].

1.4 Palliative Care

Palliative care (PC) originated from the modern hospice movement in the 1960s, which was developed to provide end-of-life (EOL) care for patients with terminal illnesses. Initially, its primary aim was to ensure comfort, dignity, and relief from suffering for individuals in the final stages of life, when curative treatment was no longer effective or appropriate.

From the 1960s until just over a decade ago, palliative care was typically introduced only at the end stage of cancer, often when patients were hospitalized due to disease progression. The focus was on symptom control, preparing for death, and arranging hospice admission.

This late intervention addressed physical suffering, but often neglected the emotional, relational, and spiritual dimensions of the person.

Worse, it contributed to the persistent misconception that **palliative care equals end-of-life care.**

Today, that model has shifted significantly.

Over the following decades, palliative care underwent a substantial evolution. It progressively moved beyond its original exclusive focus on end-of-life support and expanded its scope to earlier phases of disease, proactively supporting patients and caregivers facing a life-threatening illness from the time of diagnosis [28].

Today, palliative care is recognized by major health organizations, including the World Health Organization, as an essential component of universal health coverage. According to the WHO:

> *"Palliative care is an approach that improves the quality of life of patients (adults and children) and their families who are facing problems associated with life-threatening illness. It prevents and relieves suffering through the early identification, correct assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual. [...] Palliative care is explicitly recognized under the human right to health."*

(World Health Organization – Palliative Care Definition)

Building on the discussion of prognosis and survival in patients with hematologic malignancies, patients are often confronted with the difficult choice of pursuing prolonged overall survival (OS) at the cost of increased hospitalizations and treatment-related burden, frequently in the absence of a curative outcome. In parallel, hematologists are required to carefully evaluate whether the expected benefits and safety profiles of novel targeted therapies are consistent with patients' values, preferences, and desired quality of life (QoL).

This underscores the **importance of actively involving patients in the decision-making process**.

Notably, **greater patient involvement in decision-making has been associated with higher perceived quality of care and overall satisfaction**. This is particularly **relevant** in **hematologic malignancies**, diseases often characterized by a **complex and burdensome clinical course**, including **severe symptoms**, **psychological distress**, and frequent or prolonged **hospitalizations** often culminating in the need for **intensive support** as patients and caregivers approach the **end of life** [13].

Table 1.1: Symptom burden and its management throughout the AML course. Adapted from: *Palliative care interventions and their early integration in the management of older adults with acute myeloid leukemia: a narrative review* [13].

Symptom	Management
Anorexia/cachexia	Dietary interventions and nutritional support
Anxiety	Psychological counseling, symptom control, and use of anxiolytics when indicated
Decreased sexual interest	Psychological support, sexological counseling, and endocrinological evaluation
Xerostomia	Management of oral mucositis, adequate hydration, and use of saliva substitutes or stimulants
Dyspnea	Treatment of underlying causes (e.g., pneumonia) and transfusion support in case of anemia
Fatigue	Multimodal strategies, including exercise when feasible and transfusion support if indicated

Symptom	Management
Hair loss	Gentle hair and scalp care, scalp cooling when appropriate, use of head coverings, and emotional support
Nausea	Administration of antiemetic therapy
Pain	Comprehensive assessment of etiology and intensity, disease-directed treatment, and appropriate analgesic therapy
Sadness/depressive symptoms	Professional psychological or psychiatric support when symptoms persist and impair daily functioning
Insomnia	Identification and treatment of underlying causes (e.g., pain), lifestyle measures, relaxation techniques, and pharmacological therapy if needed
Swallowing difficulties	Dietary modifications (e.g., soft or liquid foods); enteral feeding when necessary
Swollen limbs	Compression therapy, limb elevation, sodium restriction, diuretics, and supportive measures
Urinary problems	Management of underlying causes, treatment of contributing conditions, and catheterization when required

It is now clear that patients with hematologic malignancies (HMs) have **significant palliative care needs** (Table 1.1 and Sections 1.1.2, 1.2.2, 1.3.2 of the present paper).

PC's role extends beyond advanced disease stages or situations in which curative options are no longer available, and it should ideally be introduced early and maintained throughout the entire disease trajectory. Evidence indicates that early integration of palliative supportive care (ePSC), from diagnosis through treatment initiation and up to EOL, can significantly improve the QoL of patients throughout the course of the illness [13].

Over the past decade, palliative care has been offered increasingly earlier in the course of advanced cancer, typically at diagnosis and predominantly in outpatient settings. And thats exactly why its come to be known as ***early*** palliative care

So what evidence do we have that this earlier approach actually works?

This evolution is supported by strong evidence.

Since 2009, more than 20 randomized controlled trials have compared early palliative care to standard oncology care in patients with advanced solid tumors.

These trials demonstrated multiple benefits:

- One of the **first** and most important benefits was actually the way the early studies were designed. These trials played a key role in reshaping the concept of palliative care. At the time, there was no clear framework for integrating it into the treatment of ambulatory patients who were not imminently dying, yet still faced significant physical, psychosocial, and spiritual burdens related to their illness.
- **Second**: Improved Quality of Life

  A pooled analysis of 15 randomized controlled trials showed a mean improvement of 4.59 points in quality of life scores within the first 13 months of intervention.
- **Third**: Reduced Symptom Burden

  Again in the analysis of 7 trials Symptom intensity scores were 35.4 points lower among patients receiving early palliative care. And also the management
- **Forth**: Reduced psychological symptoms

  Depressive symptoms improved by a mean of 0.98 points based on data from five studies (By conventional criteria, an Standardized Mean Difference of 0.2 represents a small effect, 0.5 a moderate effect,and 0.8 a large effect).
- **Fifth**: Survival benefit

  Three randomized controlled trials showed a survival gain ranging from 2.7 to 6.5 months, affecting 6/15% of patients.

We have compelling evidence that early palliative care improves outcomes in solid tumors.

But can we apply the same model to hematologic malignancies?

Hematologic cancers are uniquely challenging, because there are a **highly heterogeneous** group of diseases. They often follow **non-linear**, **unpredictable** courses.

This is the research context within which the present study is situated and these are the questions it seeks to address.

Before examining these questions in detail, it is important to provide an overview of the evidence generated so far regarding early palliative supportive care interventions and their impact on patient outcomes, first described in patients with solid tumors and subsequently investigated in patients with hematological malignancies.

1.5 Early Palliative Supportive Care (ePSC)

ePSC refers to palliative care delivered earlier in the disease trajectory, an approach that can further enhance patient management by preserving QoL during the course of severe and life-threatening conditions [13].

The positive impact of early palliative care interventions in advanced cancer patients has so far been **largely evaluated** in randomised controlled trials and several prospective or retrospective cohort studies. A retrospective observational study conducted on 292 advanced cancer patients published by Bandieri and coworkers in 2020 concluded that an earlier palliative/supportive care intervention was associated with **reduced aggressiveness of therapy** and **reduced symptom burden** [12].

As the incidence of AML (and HMs in general) continues to increase, the integration of ePSC into routine hematological practice has become progressively more relevant and necessary [13].

Even though there is now convincing evidence demonstrating the benefits of integrating ePSC into standard oncological treatment for patients with advanced solid tumors, for the potential value of ePSC in patients with hematological malignancies there is still a paucity of evidence-based data [10, 11, 13].

1.5.1 Early Palliative Supportive Care in Solid Cancer Patients

Among patients with metastatic non-small-cell lung cancer, early palliative care led to significant **improvements in both quality of life and mood**. As compared with patients receiving standard care, patients receiving early palliative care had **less aggressive care at end of life** but **longer survival**.

Therefore, major oncology societies, including the American Society of Clinical Oncology (ASCO), endorse its early integration as a standard element of oncologic care [10, 11, 13].

Early Palliative Supportive Care and Patients' Survival

A landmark study was conducted on 151 patients with metastatic non-small-cell lung cancer (NSCLC) by Temel et al. and published in the *New England Journal of Medicine* in 2010. Participants completed baseline questionnaires before randomization and follow-up assessments of quality of life and mood were performed at 12 weeks. The average number of visits in the palliative care group was 4 (range, 0–8).

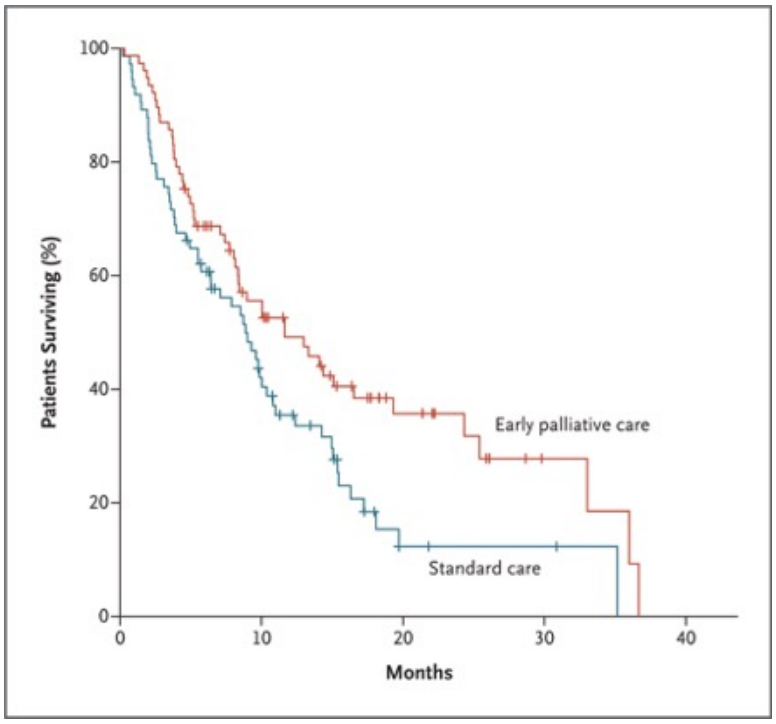

Figure 1.5: Kaplan–Meier estimates of survival according to study group. *Source: The New England Journal of Medicine* [10].

Despite receiving less aggressive end-of-life care, patients in the palliative care group had significantly longer survival than those in the standard care group (median survival, 11.6 vs. 8.9 months; $p = 0.02$) (Figure 1.5) [10].

Components of Early Palliative Supportive Care

In 2011, Jacobsen et al. published in the *Journal of Palliative Medicine* the first ever study that prospectively examined the components of an early palliative care consultation. 151 eligible patients with metastatic NSCLC were enrolled and randomly assigned to standard care or early palliative care. Seven palliative care clinicians provided consultation to 67 patients. The median total time for the initial visit was 55 minutes (range, 20–120).

From the study, it has emerged that a large portion of the initial palliative care visits was dedicated to **(1) symptom assessment**. This allowed the palliative care practitioner time to build rapport before broaching more difficult topics, such as prognosis and end-of-life decision making [18].

In addition to symptom management, approximately a third of visit time was spent exploring and supporting **(2) patient and family coping**. Results from a pilot study suggest a trend toward reduced anxiety and depression, alongside improvements in functional status and EOL preparedness preparedness among patients who participated in discussions addressing the psychosocial and spiritual aspects of their illness experience. [18, 19].

Finally, a significant proportion of visit time was spent assessing the patient's **(3) illness understanding** and their **(4) information preferences**: some patients wanted explicit prognostic information, others preferred a "big picture" approach, and others preferred not to be told their prognosis [18].

A subsequent qualitative study by Yoong and coworkers published in *JAMA Internal Medicine* in 2013 extracted data from the PC visit clinical documentation for each patient. Twenty intervention participants were randomly selected from four prognostic groups based on survival times of (1) less than 3 months, (2) 3–6 months, (3) 6–12 months, and (4) 12–24 months. The consultations were divided into first visits, middle visits, and final visits.

Seven major themes emerged from the clinical documentation: (1) relationship and rapport building, (2) addressing symptoms, (3) addressing coping, (4) establishing illness understanding, (5) discussing cancer treatments, (6) end-of-life planning, and (7) engaging family members.

It was also found that palliative care clinicians tend to **adjust the focus of care according to the phase of the illness trajectory**. During early visits, emphasis was primarily placed on building a therapeutic relationship, fostering illness understanding, and discussing the impact of cancer treatments. During final visits, the focus shifted predominantly to end-of-life planning [14].

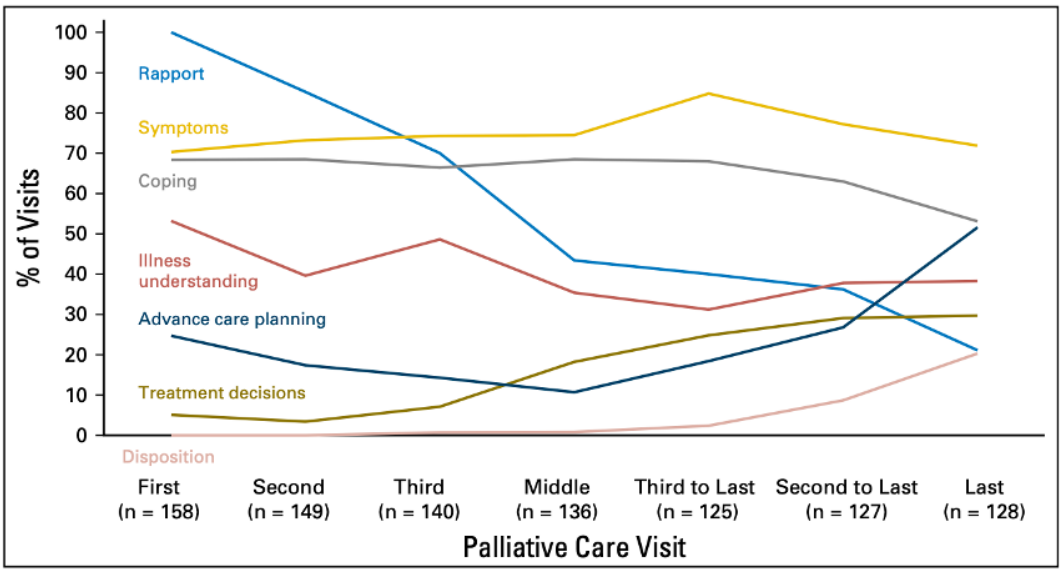

Figure 1.6: Content of palliative care (PC) visits across the illness trajectory. PC clinicians recorded the content they addressed after each visit. *Source: Yoong et al., JAMA Internal Medicine* [14].

Early Palliative Supportive Care and Patient-Reported Outcomes

A particularly relevant study is the paper published in the *Journal of Clinical Oncology* by Hoerger and coworkers in 2018, **the first ever study to link the content of PC visits to patient-reported outcomes and end-of-life care**, elucidating the potential mechanisms by which early PC improves patients' outcomes [17].

The FDA defines PROs as "a measurement based on a report that comes directly from the patient about the status of a patient's health condition, without amendment or interpretation of the patient's response by a clinician or anyone else". Accordingly, PROMs are standardized questionnaires that directly collect patient-reported health outcomes and are widely used in healthcare research to evaluate new treatments, supportive care interventions, and the overall quality of care [25].

In the study, 2,921 PC visits were analyzed, most of which addressed coping (64.2%) and symptom management (74.5%). By 24 weeks, a higher proportion of palliative care visits focused on coping was associated with better patient outcomes, including improved quality of life and reduced depressive symptoms, as measured by validated scales (HADS-D and PHQ-9). In contrast, when a greater share of visits addressed treatment decisions, patients were less likely to receive chemotherapy or be hospitalized in the final 60 days of life. Similarly, a higher emphasis on advance care planning was linked to increased use of hospice services, **suggesting that the content of early palliative care discussions may meaningfully influence both psychological outcomes and end-of-life care trajectories** [17].

Team-Based Outpatient Early Palliative Care

In 2019, Zimmermann published in *BMJ Supportive & Palliative Care* a systematic evaluation describing the components of **"Team-Based Outpatient Early Palliative Care" (TO-EPC)**, a complex intervention developed based on palliative care theory, review of previous palliative care interventions, and practice guidelines.

Such components emerged by the cluster randomized controlled trial performed by the same group in 2014.

That study included 461 patients with advanced cancer comparing TO-EPC with standard oncology care. Results showed that the **intervention group** achieved significantly **better outcomes** in terms of **quality of life**, **symptom control**, and **satisfaction with care** for both **patients** and **caregivers** [15].

> Patients and caregivers identified **four main benefits**: (1) timely and individualized symptom control, (2) comprehensive psychosocial support, (3) assistance in decision-making, and (4) preparation for the future [15].

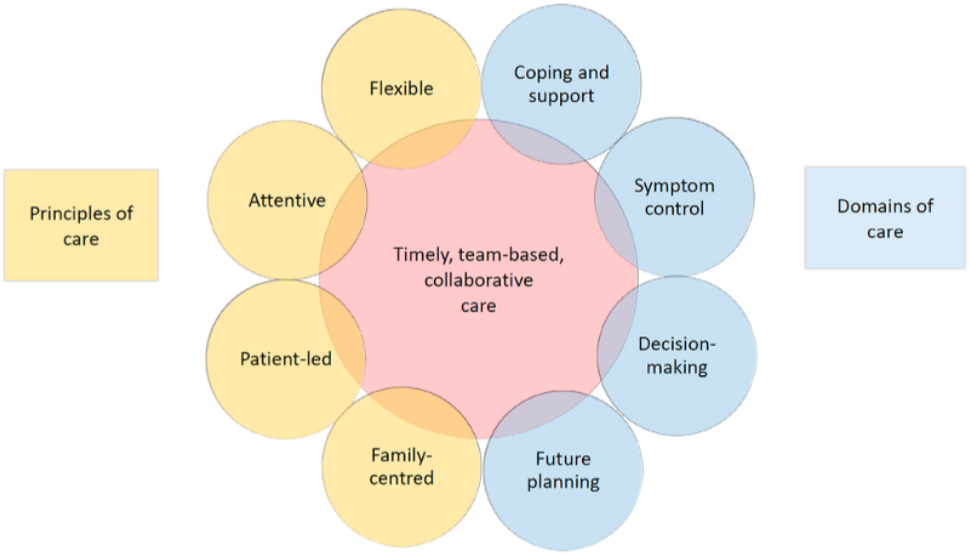

Figure 1.7: Outline of conceptual framework for TO-EPC (Team-Based Outpatient Early Palliative Care). *Source: Zimmermann C et al., BMJ Supportive & Palliative Care, 2019* [15].

1.5.2 Early Palliative Supportive Care in Hematological Malignancy Patients

This model of care has been **challenging** to implement in patients with hematological malignancies (HMs), who are exposed to highly intensive treatments with curative intent, frequently experience prolonged hospitalizations, and have traditionally received palliative care only during the end-of-life phase. In addition, HM trajectories are often characterized by considerable prognostic uncertainty, sudden clinical deterioration, and the possibility of achieving remission even after multiple relapses, making it difficult to identify the optimal timing for palliative care referral [10, 11, 13].

Nevertheless, over the last decade, growing evidence has demonstrated that early palliative supportive care can provide substantial benefits also in patients with hematological malignancies.

Early Palliative Supportive Care and Patient-Reported Outcomes

One of the first randomized controlled trials evaluating the integration of palliative care in hematology was conducted by El-Jawahri and colleagues and published in *JAMA Oncology* in 2016. [40]

The study enrolled 160 patients with hematological malignancies admitted for either autologous or allogeneic hematopoietic stem cell transplantation (HSCT) at Massachusetts General Hospital. [40]

Patients were randomly assigned in a 1:1 ratio to receive either standard transplant care alone or standard transplant care integrated with an inpatient palliative care intervention.

HSCT is among the most intensive treatments in hematology and is frequently associated with severe physical symptoms, psychological distress, prolonged hospitalization, and a marked deterioration in quality of life.

The palliative care intervention consisted of regular consultations with specialist palliative care physicians throughout the hospitalization period, focusing on symptom management, psychological support, coping strategies, and communication with patients and families.

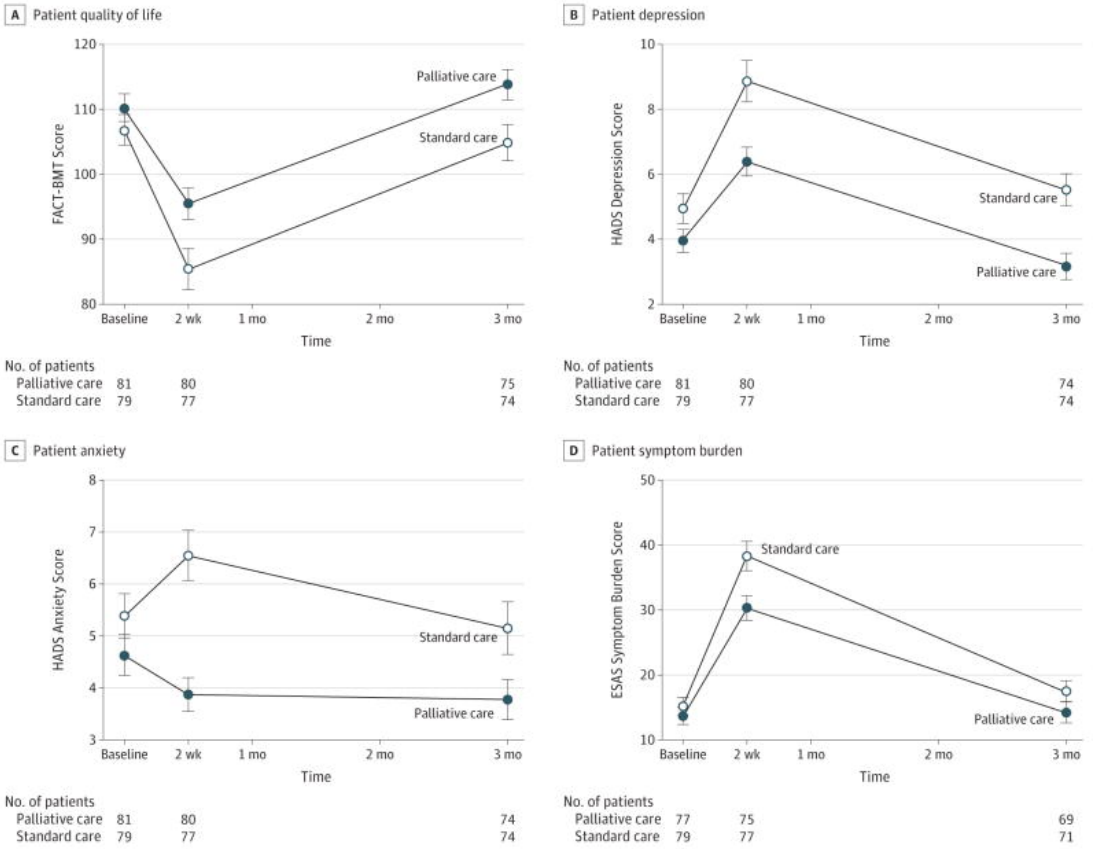

Figure 1.8: Patient-Reported Quality of Life, Depression, Anxiety, and Symptom Burden Outcomes Across All Time Points by Treatment Group

Source: El-Jawahri A et al., JAMA Oncology, 2016 [40].

The study (Figure 1.12) demonstrated that patients receiving integrated palliative care experienced a (1) significantly **smaller decline in quality of life** two weeks after transplantation compared with patients receiving standard transplant care alone. In addition, they reported (2) **lower symptom burden**, (3) fewer symptoms of **anxiety** and **depression**, and (4) **better overall psychological well-being**.

Importantly, many of these benefits persisted at three months after transplantation, suggesting that the positive effects of the intervention extended beyond the hospitalization period. [40]

This trial represented a landmark study in hematologic oncology because it demonstrated that palliative care can be successfully integrated alongside highly intensive and potentially curative treatments, providing meaningful benefits without interfering with disease-directed therapy.

Further evidence was provided by a subsequent multicenter randomized clinical trial conducted always by El-Jawahri and colleagues and published in *JAMA Oncology* in 2021. The study enrolled 160 adults with newly diagnosed acute myeloid leukemia (AML) receiving intensive chemotherapy across four tertiary academic centers in the United States. [26]

86 patients were assigned to integrated palliative and oncology care, whereas 74 received usual hematologic care. Patients in the intervention arm were evaluated by palliative care specialists at least twice weekly during their initial and subsequent hospitalizations.

The primary endpoint of the study was **quality of life at two weeks**, assessed through validated patient-reported outcome measures (PROMs).

They used:

1. the 44-item **Functional Assessment of Cancer Therapy–Leukemia** (FACT-Leu) scale (score range 0–176; higher scores = better QOL);
2. the **Hospital Anxiety and Depression Scale** (HADS), with subscale scores ranging from 0 to 21 and cut-off scores >7 indicating clinically significant symptoms;
3. the 9-item **Patient Health Questionnaire** (PHQ-9) for major depressive disorder;
4. the revised 10-item **Edmonton Symptom Assessment Scale** (ESAS) (score range 0–100; higher scores = greater symptom burden);
5. the 17-item **PTSD Checklist–Civilian Version** (score range 17–85; higher scores = worse PTSD symptoms).

When compared with patients receiving UC, patients assigned to IPC reported **better QOL** ($\beta = 2.35$; 95% CI, 0.02–4.68; $p = .048$), **lower depression** (HADS: $\beta = -0.42$; 95% CI, −0.82 to −0.02; $p = .04$), **lower anxiety** ($\beta = -0.38$; 95% CI, −0.75 to −0.01; $p = .04$), and **lower PTSD symptoms** ($\beta = -1.43$; 95% CI, −2.34 to −0.54; $p = .002$) longitudinally [26].

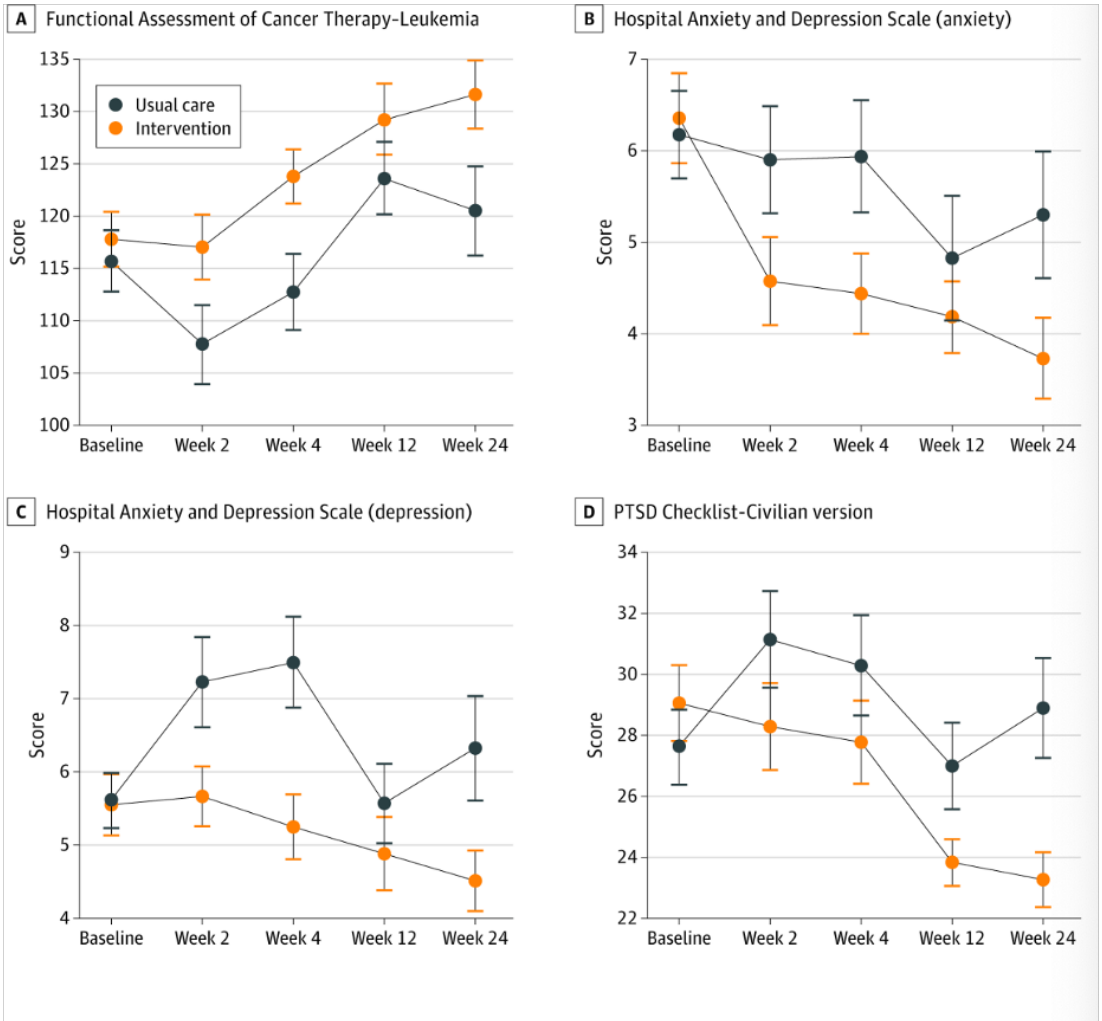

Figure 1.9: Longitudinal comparison between IPC and UC patient-reported outcomes. *Source: El-Jawahri A et al., JAMA Oncology, 2021* [26].

Patients receiving the palliative care intervention also experienced improvements in critical EOL outcomes. Specifically, patients receiving the intervention were more likely to discuss their EOL care preferences with their clinicians and less likely to use chemotherapy in the last month of life.

Discussing the same topic, but in an **outpatient setting**, in 2021, Potenza and our research group published in *BMJ Supportive & Palliative Care* an observational, retrospective study based on 131 patients with AML previously enrolled at the ePSC clinic of the Section of Hematology, AOU Policlinico, University of Modena and Reggio Emilia, from 1 January 2014 to 1 September 2019 [11].

In all patients (n=131), a structured assessment and management of physical symptoms was performed, and 72 out of 131 patients (55.0%) also received psychological support.

Patients included in the ePSC pathway showed a **statistically significant reduction in pain intensity over time**, observed consistently across all analysed time points ($p < 0.01$).

Regarding EOL care outcomes, in the last **14**, **30**, and **90 days of life**, chemotherapy was administered to **2** (2.7%), **7** (9.3%), and **19** (25.3%) **patients**, respectively, **compared with 65.9% patients** that underwent chemotherapy in the last 30 days of life **receiving standard of care** in the sole multisite randomised trial published so far [26].

Importantly, **none of the patients enrolled in the ePSC program required admission to the intensive care unit, cardiopulmonary resuscitation, or endotracheal intubation during the final month of life.** Moreover, only a very small proportion of patients (4%) experienced repeated hospital admissions or two or more emergency department visits in the last 30 days of life [11].

A previous study on 43 patients with AML had already shown that palliative care consultation was associated with a reduction in ICU admissions in the last 30 days of life (7%) and an increase in home-care use (30%), although more than half of patients still died in acute care settings (53.5%). [25]

In comparison, the results of Potenza's study suggest that earlier integration of palliative care along the disease trajectory may **further improve** these outcomes, with **no ICU admissions** (0% vs 7%), a substantially higher use of home-care services (64% vs 30%), and a markedly **lower proportion of deaths occurring in acute facilities** (5.3% vs 53.5%). [11, 25].

Together, these studies demonstrated that **the benefits of early palliative supportive care previously observed in patients with advanced solid tumors can also be achieved in hematological malignancies.** Improvements in quality of life, psychological well-being, coping abilities, symptom burden, and end-of-life care outcomes strongly support the integration of palliative care alongside active hematologic treatments.

However, although randomized trials clearly demonstrated the effectiveness of ePSC, an important question remained unanswered:

Which specific components of the intervention are responsible for these benefits?

Understanding the content of ePSC consultations is essential not only to clarify the mechanisms through which the intervention improves patient outcomes, but also to facilitate the **standardization**, **replication**, and wider **implementation** of this model of care.

In solid tumors, as it was largely discussed in the 1.5.1 section of the present work, several studies have attempted to identify the key components of early palliative care consultations, but evidence regarding the specific components of ePSC in hematological malignancies remains limited.

Components of Early Palliative Supportive Care in Hematological Malignancies

In a 2024 *BMJ Supportive & Palliative Care* publication from our research group, a detailed **description of ePSC integration in the HM setting** was presented [16].

The primary goals of the **initial ePSC visits** are to establish a trusting relationship with the patient and to carry out a thorough **assessment of their symptoms**.

Addressing and relieving symptoms plays a crucial role, as it leads to four key outcomes: (1) it improves QoL, (2) fosters the development of a strong therapeutic alliance, (3) enhances patients' problem-solving abilities and self-awareness, and (4) supports their capacity to cope with illness. Together, these benefits **create a foundation of trust and stability**, which is essential for gradually introducing more complex and sensitive discussions, such as prognosis and end-of-life planning [15–17].

Once symptoms are adequately managed, the focus can shift to **assessing the patient's awareness and understanding of their prognosis**. The **intermediate phase** of ePSC visits becomes an opportunity to **broaden the patient's perspective on hope and to support living well despite the illness**. Strengthening coping strategies during this stage can further enhance QoL, alleviate psychological distress, and gradually create the conditions for a deeper and more open awareness of prognosis [15–17].

The aim of the **final ePSC visits** is to **address end-of-life planning**. This is a personalized and evolving process that often unfolds over multiple encounters, as the patient's awareness of their prognosis gradually deepens. Although many patients struggle to fully accept the inevitability of death, they often find that ongoing, periodic conversations about this topic help them come to terms with it over time.[16]

The trajectory of illness can influence how these discussions are approached. Solid tumors generally follow a more predictable course, allowing more time to support patients in preparing for the end of life. In contrast, hematologic malignancies (HM) are often characterized by a rapid and steep decline, leaving less time for gradual preparation. For this reason, **palliative care specialists need to be ready to navigate sudden and emotionally challenging conversations**. These discussions are crucial, as they can ease distress for both patients and their families and help avoid overly aggressive interventions at the end of life. [16].

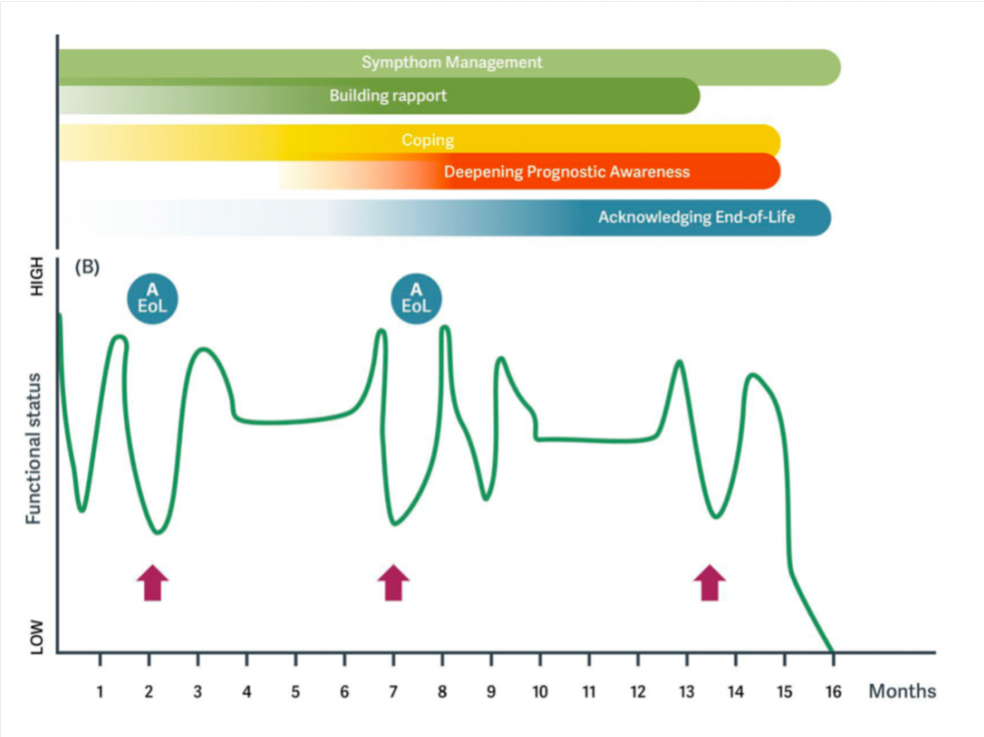

Figure 1.10: Early palliative care in hematological malignancies. *Source: Potenza L et al., British Medical Journal, 2024* [16].

In Figure 1.8, the elements of early palliative care across the illness trajectory of high-risk myelodysplastic syndrome are reported and red arrows indicate risk of sudden death during treatment. [16]

In a 2022 publication that discussed the early integration of palliative care for patients with HMs, Adir Shaulov et al. had already addressed the same issue, bringing to attention how, in contrast with solid tumors, which follow a more predictable disease course, with the development of metastases usually associated with incurability and a relatively steady clinical decline, hematological malignancies tend to have a heterogeneous and less predictable disease course.

To overcome this impediment, they divided HMs into three main groups based on the trajectory of disease, setting of care and challenges to PC delivery.

> However, although the three groups mentioned below provide a useful framework to understand the complexities of these diseases, the behavior of various HMs is heterogeneous and does not adhere rigidly to this categorization. [28]

Figure 1.9 illustrates the main disease trajectories of the three HMs groups, copmared with the trajectory of solid tumors:

- **Aggressive HM trajectory (B)** (acute leukemia, aggressive lymphoma, stem cell transplantation): high risk of harm along with realistic possibility of long-term cure. The razoredge character of these diseases makes prognosis difficult until late in the course of the disease. Often, cure may still be a reasonable and achievable goal until days before death. The rollercoaster nature of life in the context of these diseases also presents unique challenges, both physical and psychological.
- **Indolent HM trajectory (C)** (indolent lymphoma, multiple myeloma, chronic lymphocytic leukemia): incurable but longer prognosis, with episodes of decreased function due to multiple relapses and prolonged remissions. It is difficult to decide whether further treatment may be effective or detrimental to quality of life.
- **Bone marrow failure (D)** (myelodysplasia, myelofibrosis): characterized by cytopenias. Severe anemia often leads to a reliance on blood transfusions to relieve symptoms such as fatigue, shortness of breath, and chest pain. Likewise, marked thrombocytopenia can cause mild to life-threatening bleeding; regular platelet transfusions can help reduce these risks. Most critically, profound neutropenia associated with chronic, progressive bone marrow failure predisposes patients to recurrent bacterial and

invasive fungal infections. These complications are both debilitating and life-threatening, and unlike anemia and thrombocytopenia, they cannot be effectively managed with transfusion support. In this group, prognostication is again a challenge, as death is the result of acute complications of cytopenias rather than disease progression.

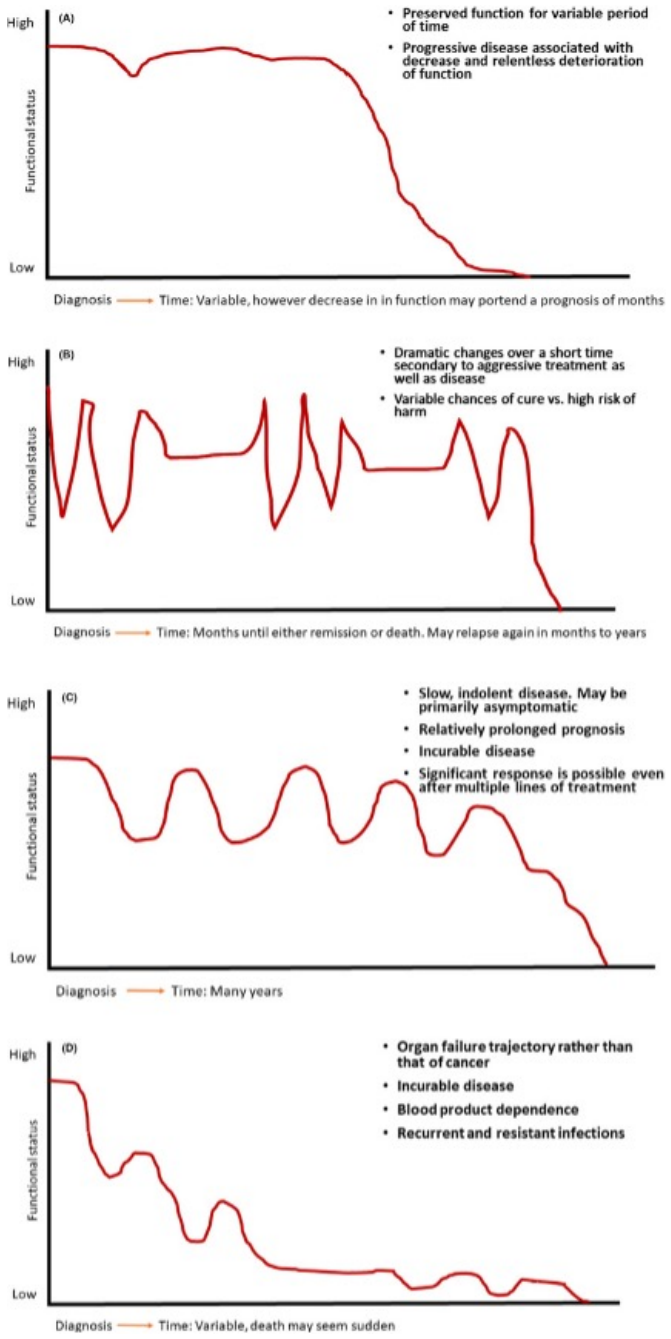

Figure 1.11: HM disease trajectories compared with solid tumor trajectory. *Source: Shaulov A, British Journal of Haematology, 2022* [28].

Compared with patients affected by solid tumors, those with hematological malignancies experience a higher frequency of emergency department visits, hospitalizations, and ICU admissions, as well as a greater use of chemotherapy and targeted therapies at the end of life. Moreover, according to most haemato-oncologists, discussions regarding end-of-life care tend to occur too late, with palliative care often being introduced only when death is imminent. In addition, patients with hematological malignancies are less likely to have an existing opioid prescription at the time of hospice admission, suggesting that symptom control may be insufficient. [28]

The most recent study that analyzes the components of ePSC consultations is a retrospective single-center study, conducted by Potenza and our research team and published on the *Journal of Pain and Symptom Management* in 2026.

The study evaluated the **implementation and outcomes of early palliative care (EPC) integrated into the management of patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndromes (HR-MDS).**

The study included 180 eligible patients who received EPC between 2013 and 2024. Overall, 1,175 outpatient EPC visits were analyzed, manually reviewing the electronic medical records (EMRs) of all patients in the study cohort, from the first EPC consultation to the end of follow-up or death. The median of visits per patient was 6 and the median time from diagnosis to the first palliative care consultation was 0.92 months, demonstrating early integration of supportive care into routine hematologic practice.

Analysis of EPC consultations identified seven principal domains of care, accordingly with the prewious literature regarding solid cancer patients [14]. The most frequently addressed component was (1) **symptom management**, documented in 89.9% of visits, followed by (2) **coping support** (74.6%), (3) **illness understanding** (71.2%), (4) **treatment discussions** (57.4%), (5) **relationship and rapport building** (52.2%), (6) **family engagement** (52.0%), and (7) **end-of-life (EOL) planning** (26.8%). [36]

The content of EPC consultations changed significantly throughout the disease trajectory. During the first three visits, relationship and rapport building was discussed in 98.5% of encounters, but this proportion decreased to 5.3% during the last three visits (p<0.001). In contrast, discussions regarding EOL planning increased markedly from 11.0% of early visits to 51.3% of late visits (p<0.001). Family involvement also increased significantly from 45.2% to 56.6% (p=0.029). Coping support became more prominent over time, rising from 65.1% to 81.0% of visits (p<0.001), whereas symptom management remained consistently frequent throughout the disease course (82.7% vs 82.5%; p=0.928). [36]

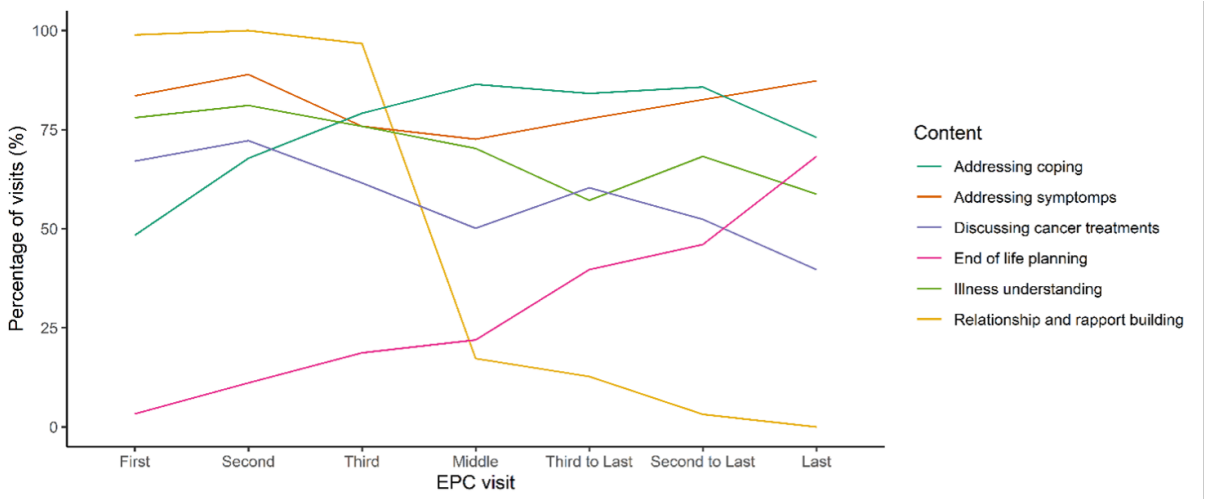

Figure 1.12: Temporal patterns of EPC components across the disease trajectory *Source: Potenza et al. Journal of Pain and Symptom Management, 2026,* [36].

Palliative care quality was evaluated using five predefined indicators derived from validated palliative care quality frameworks: (1) psychological or psychiatric support, (2) goals-of-care (GOC) conversations, (3) prognostic awareness discussions, (4) advance care planning (ACP), and (5) referral to home care services.

Quality-of-care indicators improved substantially over time. The proportion of visits documenting at least one palliative care quality indicator increased from 55.2% during the first three visits to 78.3% during the last three visits (p<0.001). Goals-of-care (GOC) conversations increased from 26.1% to 54.0% (p<0.001), while advance care planning (ACP) documentation rose from 2.2% to 21.7% (p<0.001). Referrals to home care services also increased significantly, from 4.8% to 15.3% (p<0.001). [36]

The study further demonstrated **associations between EPC exposure and less aggressive end-of-life care.** Indicators of EOL care aggressiveness were assessed for patients who died during the observation period based on established criteria and were aligned with measures rated as acceptable by hematologists both in the United States and in Italy [36–39]. These included administration of chemotherapy or targeted therapies within 90, 60, 30, or 14 days prior to death (excluding hydroxyurea for leukocyte count control); ICU admission, emergency department visits, or hospital admissions within the last 30 days of life; cardiopulmonary resuscitation or intubation within the last 30 days of life; hospice enrolment for fewer than 7 days; and in-hospital death. [36–38]

A higher number of EPC visits was associated with a lower likelihood of receiving chemotherapy in the last 30 days of life (OR 0.73; 95% CI: 0.531.00; p =.049), particularly with more visits focused on relationship and rapport building (OR 0.52; 95% CI: 0.290.95; p =.032) and symptom management (OR 0.63; 95% CI: 0.410.96; p =.033). Similarly, in-hospital death was less likely with a higher number of EPC visits and with more visits focused on symptoms (OR 0.81; 95% CI: 0.660.99; p =.038), coping (OR 0.77; 95% CI: 0.630.94; p =.010), or EOL planning (OR 0.62; 95% CI: 0.410.95; p =.028) [36]

Overall, the findings indicate that EPC in AML and HR-MDS functions as a dynamic and adaptive intervention. Early consultations are predominantly focused on symptom control, psychological adaptation, and disease understanding, whereas later encounters increasingly address advance care planning, family involvement, and end-of-life decision-making. Importantly, higher exposure to EPC and greater attention to EOL planning were associated with improved quality-of-care indicators and less aggressive care near death, supporting the early integration of palliative care into routine hematologic practice. [36]

Prospects

As knowledge of the biology of hematological malignancies and the development of targeted therapies continue to advance, patients will increasingly face challenges related to maintaining quality of life and making treatment decisions within a context of persistent prognostic uncertainty. In this setting, the interdisciplinary and holistic nature of palliative care represents a valuable resource.

A greater understanding of palliative care among haemato-oncologists, together with the development of more effective models for its integration at the tertiary level, is essential for improving the quality of care offered to this still underserved patient population [28].

1.6 Aim of the Present Thesis

Our research is focused on **exploring the content of early outpatient palliative supportive care (ePSC) consultations**, delivered within the model of care provided for patients with hematological malignancies at the section of Hematology, Azienda Ospedaliero-Universitaria (AOU) Policlinico, university of Modena and Reggio Emilia, Modena.

> The main goal was to **identify the domains of care** according to previous literature and to **examine how these topics are addressed in real-life clinical practice**.

This work builds upon our recently completed observational study, in which the content of 1,175 ePSC consultations delivered to 180 patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndromes (HR-MDS) was retrospectively reconstructed through systematic review of electronic medical records.

That study demonstrated that **ePSC consultations follow a dynamic and trajectory-adaptive model** rather than a fixed intervention.

Furthermore, the study showed that specific consultation contents were associated with established indicators of high-quality palliative care and with less aggressive care at the end of life, suggesting that **the content of ePSC interventions may be as important as the timing of their integration**.

At the same time, the study highlighted an important methodological limitation. The characterization of consultation content relied exclusively on information documented in electronic medical records.

Although clinical documentation reflects routine practice, it inevitably captures only part of the communication occurring during the consultation and may underestimate the frequency, complexity, and depth of several topics because of variability in documentation styles and selective recording of information.

In the discussion of that study, we hypothesized that **direct analysis of audio-recorded consultations could provide a more comprehensive understanding of communication processes** and validate the findings obtained through EMR-based coding.

The present thesis was therefore conceived as the natural evolution of this line of research. Instead of relying on retrospective clinical documentation, it directly analyzes real-life outpatient ePSC consultations that were prospectively audio-recorded and fully transcribed.

This methodology allows the observation of communication dynamics as they **naturally occur during patient-clinician interactions,** preserving nuances, transitions between topics, emotional exchanges, and conversational patternsthat are often only partially reflected in medical records.

An additional innovative aspect of the project is the **integration of artificial intelligence** methodologies into qualitative communication research.

In collaboration with the **UniMORE AI Center**, Tecnopolo di Modena, University of Modena and Reggio Emilia (UNIMORE), consultation transcripts are analyzed using natural language processing and machine learning techniques capable of identifying recurrent lexical clusters, semantic patterns, and thematic structures across consultations.

Beyond enabling the analysis of a large number of encounters, this approach minimizes subjective interpretation and provides a **reproducible framework** for characterizing the content and evolution of palliative care communication.

By combining, in the future, direct transcript analysis with artificial intelligence and patient-reported outcomes (PROs), this project represent a first step towards the development of a **reproducible**, **evidence-based**, and **scalable** model of integrated palliative supportive care for patients with hematological malignancies, spanning **from diagnosis through end-of-life care**.

Chapter 2

Materials and Methods

2.1 Study Design

The present study consists of a single-center qualitative observational analysis of prospectively collected data obtained between October 30, 2023, and April 5, 2025. Data were collected by one of the investigators (L.P.), consultant hematologist and palliative care clinitian at the Centro Oncologico Modenese (COM), Azienda Ospedaliero-Universitaria (AOU) Policlinico di Modena (MO)

The dataset comprised anonymized transcripts of real-world early palliative care encounters. These consultations were prospectively recorded after obtaining written informed consent from all participating patients, in accordance with ethical and regulatory requirements.

2.2 Early Palliative Care Intervention

The ePSC intervention was delivered by a multidisciplinary team of hematologists, comprising one assistant physician, one hematology fellows, specialized in providing specific supportive care with advanced training in communication skills.

The assistant physician underwent a faculty development course on VitalTalk (www.vitaltalk.org), while all others underwent communication skills training according to the same model. Based on evidence-based principles, this training model includes brief didactic sessions, demonstration of skills by faculties, intensive skill practice with simulated patients, and feedback sessions focusing on trainee needs.

The ePSC intervention was integrated into routine ambulatory evaluations during hematologic encounters, following guidelines previously established for patients with solid or hematologica cancers by our ePSC team [11, 16, 29, 36, 39]. Comprehensive symptom management and psychosocial, spiritual, and emotional support were provided to patients with HM and their families according to general guidelines and as previously reported, ensuring a standardized and reproducible interventio.

The team also facilitated the cultivation of prognostic awareness, assisted patients and families with treatment decisions, and supported coping mechanisms for dealing with life-threatening diseases. [26]

To ensure continuity of care, the ePSC team established connections with specific home-care services within the regional area and conducted regular phone calls to patients unable to attend scheduled visits or receiving exclusive home-care services. The ePSC intervention was defined as occurring within 8 weeks from diagnosis, following ASCO guidelines.[41]

2.3 Study Population and Selection Criteria

The study cohort comprised **48 patients**: 40 diagnosed with Acute Myeloid Leukemia (AML), 5 with Lymphoma (LYM), and 3 with Multiple Myeloma (MM).

All the baseline characteristics of the study population are reported in Table 2.1.

The Selection Criteria were: (1) age ≥ 18 years.; (2) diagnosis of a hematological malignancy; (3) enrollment in an outpatient early palliative care pathway, according to the care model implemented at the Section of Hematology of the Centro Oncologico Modenese (COM), AOU Policlinico, University of Modena and Reggio Emilia, Modena; (4) ability to communicate in Italian; and (5) provision of written informed consent for the audio recording of clinical encounters.

Table 2.1: Baseline characteristics of the study population

Characteristic	Value
Number of patients	48
Age in years, mean ± SD (range)	71.9 ± 6.9 (53–86)
Sex, n (%)	
Male	28 (58.3%)
Female	20 (41.7%)
Diagnosis, n (%)	
Acute Myeloid Leukemia (AML)	40 (83.3%)
Lymphoma	5 (10.4%)
Multiple Myeloma	3 (6.3%)

2.4 Collection of Outpatient Visit Transcripts

A total of **128 consultations** were included in the analysis.

The mean number of consultations per patient was 2.7 ± 1.5, with a range from 1 to 6 consultations (Supplementary Table A.1).

Following an initial set of randomly selected consultations used mainly to define the study cohort, a purposive sampling strategy was refined to **maximize the number of examples** and ensure adequate representation of the entire early palliative care (ePSC) trajectory.

Whenever possible, **multiple transcripts per patient** were included (in order to obtain a mean of three transcript per patient), with particular attention to capturing consultations from **different stages** of follow-up, from early to late visits.

> Visit number was used as an approximate indicator of the stage of the ePSC trajectory and the final sample comprised consultations distributed across multiple time points of the EPC pathway.

This approach was particularly valuable because, as extensively discussed in the previous chapters, the content of ePSC consultations is expected to evolve throughout the disease trajectory.

Previous studies have shown that early palliative care functions as a dynamic and adaptive intervention, with different communication domains becoming more or less prominent depending on the patient's clinical condition and stage of care. Early consultations tend to focus primarily on symptom management, psychological adaptation, coping strategies, and illness understanding, whereas later encounters increasingly address family involvement, advance care planning, and end-of-life decision-making [14, 17, 36].

Therefore, by ensuring the inclusion of consultations from different stages of follow-up, our objective was not only to increase the diversity of the dataset but also to investigate how the content of ePSC discussions changes over time.

This strategy allowed us to capture a **broader spectrum of communication patterns and to explore the dynamic evolution of the intervention across the patient journey**.

Furthermore, previous evidence suggests that greater exposure to ePSC and increased attention to end-of-life planning are associated with improved quality-of-care indicators and less aggressive care near death, further supporting the importance of studying **how these communication domains emerge and evolve throughout the care trajectory** [11, 36].

The frequency of analyzed consultations in our dataset according to visit number is reported in Table 2.2 and Figure 2.1.

Table 2.2: Distribution of analyzed consultations across the ePSC trajectory.

Phase of ePSC trajectory	**Consultations, n**	**Percentage (%)**
First visit (Visit 1)	11	8.0
Early visits (Visits 2–4)	38	27.5
Intermediate visits (Visits 5–7)	50	36.2
Late visits (Visits 7 +)	39	28.3
Total	138	100.0

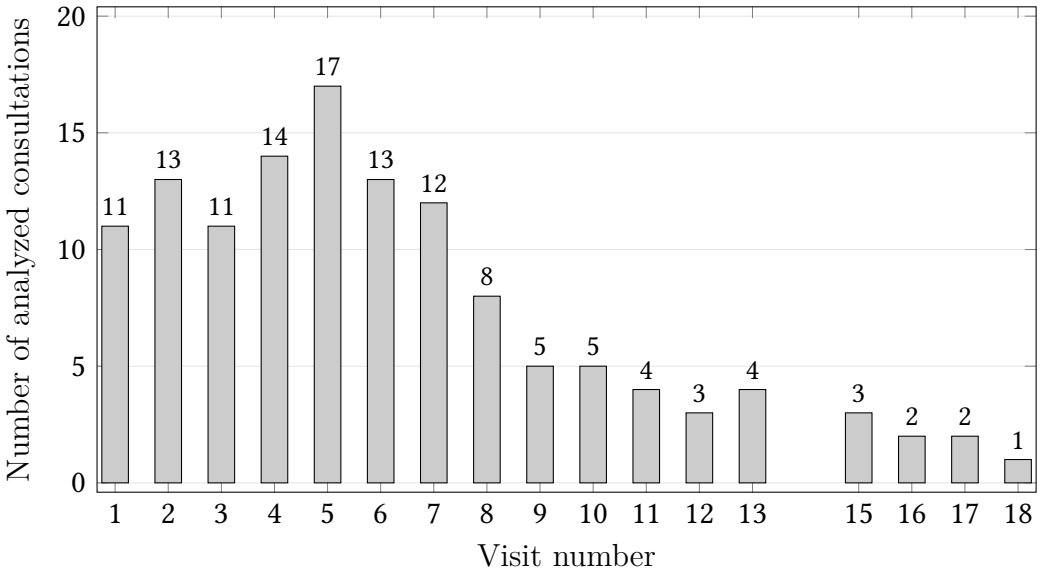

Figure 2.1: Distribution of analyzed consultations according to visit number.

All recorded consultations were subsequently transcribed manually into anonymized plain-text (.txt) documents and these transcripts constituted the dataset used for the qualitative AI analysis.

2.5 Data Anonymization and Management

To ensure participant anonymity, each patient was assigned a unique identification code (e.g., P001, P002, P003, P004 etc). In addition, each transcript was assigned a distinct identifier incorporating the patient's code and the sequential number of the consultation (e.g., P001.01, P001.02, P002.01 etc), allowing tracking while preserving anonymity.

Furthermore, during the transcription process, all potentially identifying information was removed in order to preserve participant confidentiality. Any personal identifiers, including but not limited to home addresses, names of family members, and the name of the patient's general practitioner, were systematically replaced with the placeholder XXX in the final transcripts. All study data were **fully anonymized prior to analysis**.

To further protect sensitive information, data exchange among study collaborators was performed through removable storage devices and direct offline transfer, avoiding the transmission of files through internet-based platforms.

2.6 AI-Based Analysis of Transcripts

2.6.1 Background

The availability of audio-recorded and transcribed clinical encounters offered the possibility of studying these conversations using computational methods. In this context, artificial intelligence and natural language processing may help identify recurrent communicative patterns, quantify clinically meaningful dialogue domains, and support research on patient-centered care. The present work focuses on the development and evaluation of natural language processing techniques for the analysis of palliative care conversations.

Natural Language Processing

Natural Language Processing (NLP) is a field of artificial intelligence concerned with the computational analysis, representation, and generation of human language. In medicine, NLP has been applied to a wide range of tasks, including the extraction of information from clinical notes, the classification of medical documents, the summarization of patient records, and the analysis of patient–clinician communication [31]. These applications are based on the possibility of transforming written or spoken language into numerical representations that can be processed by machine learning models.

Clinical language presents specific challenges. It often contains abbreviations, domain-specific terminology, implicit references to previous clinical events, and expressions whose meaning depends on the conversational context. In the case of palliative care conversations, the complexity is further increased by the presence of subtle communicative functions. For example, within the same short dialogue segment, a physician may address symptoms, explore patient values, support emotional coping, discuss treatment options, and promote awareness of illness progression. Therefore, NLP methods applied to this domain must be able to represent not only isolated words, but also the meaning and function of multi-turn conversations.

The starting point of this analysis is a collection of transcribed patient–physician conversations. Each transcript is first represented as an ordered sequence of utterances, where an utterance is a single speaking turn produced by one participant.

Because complete transcripts may be long and may contain multiple topics, each transcript is divided into shorter segments. In this thesis, each segment contains ten consecutive utterances and is referred to as a conversation chunk. This unit of analysis is used because it preserves local conversational context while remaining sufficiently short to be processed by current NLP models.

However, a machine learning model cannot directly interpret text in the same way as a human reader. Before a conversation chunk can be analyzed, it must be converted into a structured numerical form.

The first step in this conversion is called tokenization. Tokenization consists of dividing the text into smaller units, called tokens, that can be recognized by the model [34]. Intuitively, this process can be compared to dividing a word into syllables, because both procedures split language into smaller components. However, tokenization is more flexible and more complex than syllabification: a token may correspond to a complete word, part of a word, punctuation, a number, or a special symbol used by the model.

For example, a sentence such as:

The patient reports uncontrolled pain.

may be divided into tokens as follows:

`The | patient | reports | uncontrolled | pain | .`

In other cases, a less common or morphologically complex word may be divided into sub-word units. For instance, depending on the tokenizer, the word `uncontrolled` may be represented as:

`un | controlled`

This strategy allows the model to process rare or previously unseen words by combining smaller units that are already present in its vocabulary.

Let x_i denote the i-th conversation chunk. After tokenization, the chunk is represented as a sequence of tokens:

$$x_i \rightarrow (w_{i,1}, w_{i,2}, \ldots, w_{i,L_i}), \tag{2.1}$$

where $w_{i,j}$ denotes the j-th token of chunk x_i, and L_i is the number of tokens in the chunk.

After the text has been tokenized, each token is mapped to a vector representation, called an embedding. An embedding is a numerical vector that encodes information about the meaning and usage of a token. The sequence of token embeddings is then processed by an encoder model, which combines information across the tokens and produces a representation of the whole conversation chunk [30]. Formally, an encoder can be described as a function f_θ, with parameters θ, that maps the tokenized input into a dense vector representation:

$$\mathbf{h}_i = f_\theta(w_{i,1}, w_{i,2}, \ldots, w_{i,L_i}) \in \mathbb{R}^d, \tag{2.2}$$

where $\mathbf{h}_i$ is the representation of the conversation chunk and d is the dimensionality of the embedding space. This vector is intended to summarize the semantic and contextual information contained in the chunk.

The goal of this processing is to obtain a representation that preserves information relevant to the clinical and communicative content of the dialogue. Once a conversation chunk has been represented as a vector, several types of analyses become possible. First, chunks can be compared with each other by measuring the similarity between their embeddings. This makes it possible to explore whether conversations with similar clinical content, similar visit stages, or similar communicative functions occupy nearby regions of the representation space. Second, embeddings can be used as input to supervised learning models trained to recognize specific palliative care communication domains, such as symptom management, coping support, illness understanding, or end-of-life planning. Third, model predictions can be associated with evidence in the original text, allowing researchers and clinicians to inspect which parts of the conversation contributed to the prediction.

In this thesis, NLP methods are therefore used to transform transcribed patient–physician dialogues into numerical representations suitable for computational analysis. These representations are used in two complementary ways. The first is

exploratory: embeddings are visualized and analyzed to investigate whether conversation chunks naturally organize according to visit stage or clinical content. The second is predictive: supervised models are trained to identify clinically relevant communication domains in a multi-label setting, where more than one domain may be present in the same conversation chunk.

The Transformer Architecture

The Transformer architecture is one of the most influential neural network architectures in modern Natural Language Processing. It was introduced as an alternative to previous sequence models and is based on the attention mechanism [35]. Unlike recurrent model, that process text strictly from left to right, Transformers model the interaction between any pair of tokens in parallel.

The central mechanism of the Transformer is called *attention*. In intuitive terms, attention allows each token in a sequence to exchange information with the other tokens in a selective way, regardless of their distance in the text. This means that a word or expression can be interpreted in relation to other relevant parts of the same sentence or dialogue segment, even when they are not adjacent. This property is fundamental for creating informative textual representations, because the meaning of a token often depends on the context in which it appears.

This mechanism is particularly useful for clinical dialogue analysis. The meaning of an utterance often depends on previous turns in the conversation. For instance, the sentence “I understand” may express simple acknowledgment, emotional validation, or acceptance of prognostic information depending on the preceding patient statement.

Modern Transformer-based NLP models are usually developed in two stages. In the first stage, called *pre-training*, the model is exposed to very large collections of text. At this stage, the model is not yet trained for the specific clinical task of interest. Instead, it learns general properties of language, such as how words are used, how sentences are structured, and how meaning depends on context. In this way, pre-training provides the model with a broad linguistic foundation.

In the second stage, called *fine-tuning*, the pre-trained model is adapted to a specific task using a smaller, task-specific dataset. For example, in this thesis, a pre-trained model can be fine-tuned using annotated palliative care conversation chunks, so that it learns to associate dialogue segments with clinically relevant

communication domains. This two-step approach is particularly useful in medical applications, where manually annotated datasets are often limited in size. Instead of training a model from the beginning using only a small clinical dataset, fine-tuning allows the analysis to start from a model that has already learned general language representations.

Encoder-only Transformer Architectures

Transformer models can be broadly divided into encoder-only, decoder-only, and encoder–decoder architectures. Among these, encoder-only models are particularly relevant when the objective is to represent an input text in a form that can be analyzed or classified. Rather than generating new text, an encoder receives a sequence of tokens and transforms it into contextual numerical representations. Examples of encoder-only architectures include BERT and its biomedical or clinical variants [30].

The output of an encoder can be interpreted as an embedding of the input text. In this context, an embedding is a vector representation in which texts with related meanings or similar linguistic properties are expected to have similar numerical representations. Following the notation introduced in eq:hi, the encoder maps the tokenized input sequence into a dense vector representation $\mathbf{h}_i \in \mathbb{R}^d$. Therefore, encoder-only models are useful not only because they process text, but because they produce representations that can be compared, visualized, or used as input for subsequent predictive models.

In the present setting, an encoder-only model receives as input a chunk of patient–physician conversation and produces a contextual representation of that chunk. This representation can then be used to predict whether specific palliative care communication domains are present. Because a single dialogue chunk may contain multiple relevant domains, the task is formulated as a *multi-label classification* problem. Let K denote the number of communication domains considered in the annotation scheme. For each conversation chunk x_i, the corresponding annotation is represented by a binary vector:

$$\mathbf{y}_i = (y_{i,1}, y_{i,2}, \dots, y_{i,K}) \in \{0,1\}^K, \tag{2.3}$$

where $y_{i,k} = 1$ indicates that the k-th communication domain is present in chunk x_i, while $y_{i,k} = 0$ indicates that it is absent. Since multiple components of $\mathbf{y}_i$

can be equal to one at the same time, more than one label can be assigned to the same chunk. For example, a segment may simultaneously involve symptom management, emotional coping, and discussion of illness understanding.

The supervised model uses the encoder-derived representation $\mathbf{h}_i$ to estimate a probability for each label:

$$\hat{\mathbf{y}}_i = \sigma(\mathbf{W}\mathbf{h}_i + \mathbf{b}) \in [0,1]^K, \tag{2.4}$$

where $\mathbf{W}$ and $\mathbf{b}$ are trainable parameters of the classification layer, $\sigma(\cdot)$ denotes the sigmoid function applied independently to each output component, and $\hat{y}_{i,k}$ represents the predicted probability that the k-th communication domain is present in the chunk.

In this thesis, encoder-derived embeddings are used in two complementary ways. First, they are used for exploratory analysis, where conversation chunks are compared and visualized in the embedding space. Second, they are used for supervised classification, where models are trained to associate each chunk with one or more clinically relevant communication labels.

Unsupervised Representation Analysis

Unsupervised learning refers to a family of methods that aim to identify structure in data without using explicit target labels during training. In the context of text analysis, unsupervised methods can be used to explore whether conversation chunks with similar content are located close to each other in the embedding space. Following the notation introduced in eq:hi, each conversation chunk x_i is represented by an encoder-derived vector $\mathbf{h}_i \in \mathbb{R}^d$. The unsupervised analysis is therefore performed on the set of representations:

$$\mathscr{H} = \{\mathbf{h}_i\}_{i=1}^N, \tag{2.5}$$

where N is the total number of conversation chunks.

For this thesis, unsupervised representation analysis is used as an exploratory step.

The objective is not to make definitive clinical predictions, but to assess whether modern embedding models naturally organize palliative care conversations according to clinically meaningful variables. In particular, the analysis investigates whether chunks from later visits occupy specific regions of the embedding space. The visit number associated with chunk x_i is denoted by NUMERO VISITA EPC$_i$. Higher values of NUMERO VISITA EPC$_i$ are expected, on average, to be associated with a higher probability of containing end-of-life planning, advanced illness discussions, or treatment decision-making.

This analysis differs from the supervised multi-label classification setting introduced in equation (2). In supervised learning, the model uses expert annotations $\mathbf{y}_i$ to learn the association between a chunk and one or more communication domains. In the unsupervised setting, these labels are not used to train the representation. Instead, metadata such as NUMERO VISITA EPC$_i$ are used only after the embeddings have been computed, in order to examine whether the structure of the representation space is clinically interpretable.

It is important to emphasize that the visit number is not a precise clinical annotation. Rather, NUMERO VISITA EPC$_i$ represents a weak ordinal proxy for the stage of the patient journey. The same visit number may correspond to different clinical situations across different patients. For example, one patient may discuss end-of-life preferences early in the trajectory, whereas another patient may primarily address symptom control during a later visit. Therefore, poor separation by visit number does not necessarily indicate that the embeddings are uninformative; it may instead reflect the heterogeneity of palliative care trajectories and the imperfect correspondence between visit order and conversational content.

Dimensionality Reduction and Manifold Learning

As introduced in Equation (2), each conversation chunk x_i is represented by an encoder-derived vector $\mathbf{h}_i \in \mathbb{R}^d$. In most modern NLP models, the dimensionality d is large, meaning that each chunk is represented as a point in a high-dimensional embedding space. Although these high-dimensional vectors can be used for computational analysis, they cannot be directly visualized by a human observer. Dimensionality reduction methods are therefore used to project high-dimensional representations into a lower-dimensional space, usually two or three dimensions, while preserving meaningful relationships between data points.

Uniform Manifold Approximation and Projection (UMAP) is a commonly used dimensionality reduction method for visualizing high-dimensional data [33]. In this thesis, UMAP is applied to the set of chunk representations $\mathscr{H} = \{\mathbf{h}_i\}_{i=1}^{N}$, introduced in Section 1.4. The method learns a projection function that maps each original representation into a bidimensional vector:

$$\mathbf{z}_i = \text{UMAP}(\mathbf{h}_i), \qquad \mathbf{h}_i \in \mathbb{R}^d, \quad \mathbf{z}_i \in \mathbb{R}^2. \tag{2.6}$$

Thus, after applying UMAP, each conversation chunk is represented as a point in a two-dimensional plane and can be displayed in a scatter plot.

UMAP attempts to preserve local neighborhood structure, meaning that points close to each other in the original high-dimensional embedding space should remain close in the low-dimensional visualization. In the present study, this property is used to explore whether conversation chunks with similar semantic or clinical content tend to appear near each other in the bidimensional representation. The resulting UMAP plots are then colored according to metadata such as the visit number NUMERO VISITA EPC$_i$, allowing visual inspection of whether patterns emerge according to visit stage or other clinically relevant variables.

2.6.2 Data analysis

Data Preparation

The dataset consisted of audio-recorded conversations between patients receiving palliative care and physicians involved in their clinical management. The conversations were recorded in a clinical setting during routine encounters. All recordings were collected according to the ethical and institutional requirements of the study.

Before analysis, the audio files were transcribed into written text. When necessary, transcripts were reviewed to correct transcription errors and to preserve the structure of the dialogue.

Each transcript was divided into smaller conversation chunks, for a total of **8293 chunks** (Supplementary Table A.1).

A chunk was defined as a multi-turn dialogue segment composed of **ten consecutive utterances** (Supplementary Table A.1). An utterance corresponded to a single speaking turn by either the patient, the physician, or another participant. This chunking strategy was adopted to obtain units of analysis that were sufficiently short for computational modeling but sufficiently long to preserve conversational context.

Speaker identifiers were standardized across the transcripts. For example, abbreviations such as "M" were expanded to indicate the physician speaker, while patient utterances were explicitly marked as patient speech. This pre-processing step was necessary to make the dialogue structure interpretable by the model. Speaker information was retained because the communicative meaning of an utterance often depends on who produced it.

Since the original conversations were in Italian, the transcripts were translated into English before being processed by English-language embedding and transformer models. Translation was performed to take advantage of widely used NLP models trained primarily on English corpora.

For each chunk, metadata were retained, including the patient identifier, transcript identifier, chunk index, and visit number. The visit number, denoted as Numero Visita Epc, represented the chronological order of the visit within the patient trajectory. Higher values of Numero Visita Epc were expected to be associated with a higher probability of discussing advanced illness, end-of-life planning, or preference-sensitive decisions. However, Numero Visita Epc was treated as an approximate and patient-dependent variable rather than as a definitive clinical label.

Data Annotation

A subset of conversation chunks (n=1084 out of the 8293 total) was annotated manually by two of the authors, including me, after undergoing a training on the matter, according to clinically relevant palliative care communication domains (Supplementary Table A.1).

To identify EPC components we conducted indipendently the review process, with conversation chunks divided among authors to minimize bias.

At the beginning of the project, all authors participated in a joint training session during which a subset of annotations was collaboratively reviewed to ensure the correct interpretation of the topic(s) discussed in the utterances.

The annotation was formulated as a multi-label task, meaning that each chunk could receive more than one label. This choice reflects the nature of real clinical conversations, where several communication functions may occur within the same segment.

The labels were extracted from previous literature investigating the content of EPC consultations. Specifically, they were identified based on the frameworks proposed by Yoong et al. in 2013 [14] and Potenza et al. [36] in 2026, which analyzed the main topics addressed during EPC visits in patients with solid and hematological malignancies, respectively. The labels in the annotation scheme included the following:

1. **Relationship and rapport building**: utterances aimed at establishing trust, expressing empathy, validating emotions, maintaining connection, or strengthening the therapeutic alliance.
2. **Addressing symptoms**: discussion of physical or psychological symptoms, functional limitations, medication management, side effects, or interventions aimed at improving comfort.
3. **Addressing coping**: exploration or support of the patient's emotional, practical, or existential adjustment to illness. This includes discussion of fears, uncertainty, sources of support, resilience, and strategies used to manage the burden of disease.
4. **Illness understanding**: discussion of the patient's comprehension of the disease, prognosis, treatment response, uncertainty, or expectations about the future. This label includes both physician explanations and patient expressions of understanding.
5. **Discussing cancer treatments**: discussion of oncological treatments, including chemotherapy, immunotherapy, radiotherapy, treatment options, treatment response, treatment burden, or decisions about continuing, changing, or stopping anticancer therapy.
6. **End-of-life planning**: discussion of goals of care, hospice, comfort-focused care, advance care planning, resuscitation preferences, preferred place of

care, or decisions aimed at aligning treatment with the patient's values near the end of life.

7. **Engaging family members**: involvement of relatives or caregivers in the conversation, including discussion of family support, caregiver burden, family preferences, or shared decision-making with family members.

The annotation criteria were designed to capture communication functions rather than only topics. For example, a discussion about pain medication was annotated as **addressing symptoms**, whereas a discussion about how the patient manages fear or uncertainty was annotated as **addressing coping**. Similarly, a statement about disease progression could be annotated as **illness understanding**, while a discussion about hospice or treatment limitation could be annotated as **end-of-life planning**.

Unsupervised Learning

The first analytical objective was to explore whether state-of-the-art embedding models could generate informative representations of palliative care conversation chunks without explicit supervision. Following the notation introduced in Equation(2), each translated conversation chunk x_i was transformed into a dense vector representation:

$$\mathbf{h}_i = f_\theta(x_i) \in \mathbb{R}^d, \tag{2.7}$$

where f_θ denotes the pre-trained embedding model, $\mathbf{h}_i$ is the embedding associated with chunk x_i, and d is the dimensionality of the embedding space. In the preliminary experiments, the `e5-large` model was used to obtain semantic embeddings of the chunks.

The resulting set of embeddings,

$$\mathscr{H} = \{\mathbf{h}_i\}_{i=1}^N, \tag{2.8}$$

where N is the total number of chunks, was projected into two dimensions using UMAP, as described in Equation (6).

This produced a bidimensional representation for each chunk:

$$\mathbf{z}_i = \mathrm{UMAP}(\mathbf{h}_i), \qquad \mathbf{z}_i \in \mathbb{R}^2. \tag{2.9}$$

The UMAP visualization was then colored according to the visit number NUMERO VISITA EPC$_i$, where NUMERO VISITA EPC$_i$ denotes the visit associated with chunk x_i. This analysis was used to assess **whether chunks from similar visit stages were located in similar regions of the embedding space**, and whether the embedding model captured a latent progression related to the patient journey.

Because NUMERO VISITA EPC$_i$ is an imperfect and patient-dependent proxy for clinical stage, the analysis was interpreted as exploratory rather than confirmatory. In particular, the same value of NUMERO VISITA EPC$_i$ may correspond to different clinical situations across patients, and later visits do not necessarily contain the same communication domains in every patient trajectory.

A second analysis was performed on a subset of patients who covered all visit numbers from 1 to 11. This restricted analysis was used to investigate whether temporal patterns were more evident within individual patient trajectories than across the entire cohort. This distinction is clinically relevant because palliative care trajectories are heterogeneous, and the same visit number may correspond to different disease stages or communication needs across patients.

Supervised Learning

The second analytical objective was to train models capable of predicting the annotated palliative care communication domains. As introduced in Equation (3), each conversation chunk x_i is associated with a binary annotation vector $\mathbf{y}_i \in \{0,1\}^K$, where K is the number of communication domains considered in the annotation scheme. Each component $y_{i,k}$ indicates whether the k-th domain is present in chunk x_i. Because multiple components of $\mathbf{y}_i$ may be equal to one, the problem was formulated as a multi-label classification task.

Transformer-based encoder models were used as supervised backbones. Following the notation introduced in Equation (2), the encoder receives the tokenized conversation chunk and produces a contextual representation $\mathbf{h}_i \in \mathbb{R}^d$. This representation is then passed to a classification layer that produces one independent prediction score for each communication domain.

As described in Equation (4), the predicted label probabilities are computed as:

$$\hat{\mathbf{y}}_i = \sigma(\mathbf{W}\mathbf{h}_i + \mathbf{b}) \in [0,1]^K, \tag{2.10}$$

where $\mathbf{W}$ and $\mathbf{b}$ are trainable parameters of the classification layer, and $\sigma(\cdot)$ denotes the sigmoid function applied independently to each output component. The value $\hat{y}_{i,k}$ represents the predicted probability that the k-th communication domain is present in the chunk.

The model was trained by comparing the predicted probabilities $\hat{\mathbf{y}}_i$ with the ground-truth annotation vector $\mathbf{y}_i$. Since each label is treated as an independent binary prediction, the binary cross-entropy loss was used:

$$\mathscr{L}_{\text{BCE}} = -\frac{1}{N}\sum_{i=1}^{N}\sum_{k=1}^{K}\left[y_{i,k}\log(\hat{y}_{i,k}) + (1-y_{i,k})\log(1-\hat{y}_{i,k})\right], \tag{2.11}$$

where N is the number of training chunks. This objective allows the model to learn each communication domain separately while still assigning multiple labels to the same conversation chunk.

To adapt large transformer models efficiently, parameter-efficient fine-tuning techniques such as Low-Rank Adaptation (LoRA) were considered [31]. LoRA reduces the number of trainable parameters by introducing small trainable matrices into selected parts of the model while keeping most of the original model weights fixed. This approach is useful when the annotated dataset is limited in size or when computational resources are constrained.

Model performance was evaluated using metrics appropriate for multi-label classification. These included precision, recall, F1-score, and the area under the precision–recall curve, computed separately for each communication domain. Label-wise evaluation was considered essential because each domain represents a distinct clinical and communicative construct, and the model may perform differently across domains. Moreover, some labels may be less frequent than others, meaning that aggregate metrics could obscure poor performance on rarer but clinically important categories.

In supervised machine learning, model performance should be assessed on data that were not used during training. For this reason, the dataset is typically divided into a training set, used to optimize the model parameters, and a test set, used only for final evaluation. This separation provides an estimate of how

well the model generalizes to unseen examples, rather than only measuring how well it fits the data on which it was trained.

Specifically, patient-level data splitting was adopted to reduce the risk of information leakage. Under a patient-level split, chunks from the same patient are not simultaneously present in both the training and test sets. This is important because chunks from the same patient may share linguistic patterns, clinical history, physician style, or recurring topics. If chunks from the same patient were present in both training and test sets, model performance could be overestimated because the model might partially recognize patient-specific characteristics rather than learning generalizable communication patterns.

In addition to evaluating predictive performance, explainability analyses were considered to investigate the conversational patterns learned by the supervised models. In the context of palliative care, this step is important because model predictions should be examined in relation to clinically meaningful dialogue elements, such as symptom descriptions, emotional expressions, prognostic statements, or discussions of treatment preferences.

Attribution methods, such as gradient-based saliency or integrated gradients, can be used for this purpose. In the notation introduced above, these methods estimate which parts of the input chunk x_i most influenced a specific predicted probability $\hat{y}_{i,k}$. The resulting highlighted words, tokens, or utterances were interpreted as model-derived evidence for a prediction, rather than as definitive proof of clinical reasoning.

Chapter 3

Results

3.1 Unsupervised Learning

The unsupervised analysis showed limited separation of conversation chunks according to visit number. When embeddings from all patients were projected into two dimensions using UMAP, chunks belonging to different values of NUMERO VISITA EPC largely overlapped.

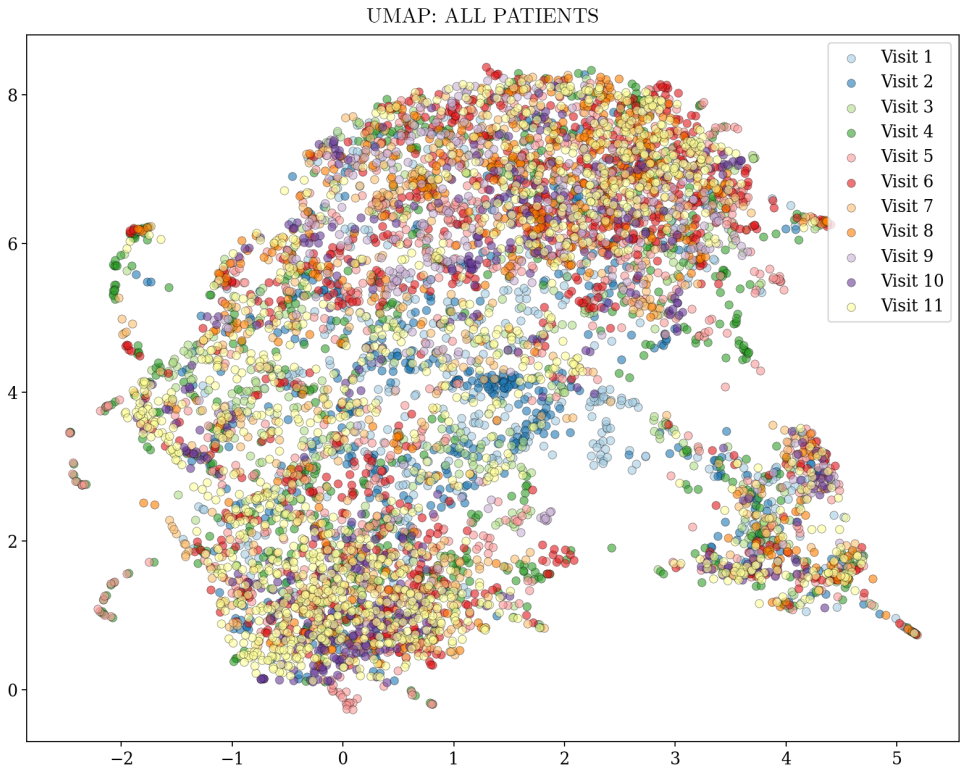

Figure 3.1: Separation of conversation chunks according to visit number. Embedding into a two dimentional space of all the patients' visits.

This result (Figure 3.1) suggests that the pre-trained embedding representations showed substantial overlap across visit numbers, suggesting that chronological visit order alone may not adequately capture the complexity and heterogeneity of communication content within ePSC encounters.

However, this finding should not be interpreted as evidence that the embeddings were clinically meaningless. Rather, it likely reflects the fact that visit number is a weak and heterogeneous proxy for palliative care content. A later visit may contain routine symptom management, while an earlier visit may already include discussions of prognosis or end-of-life concerns. Therefore, substantial overlap between visit stages is clinically plausible.

In the restricted analysis including only patients with visits spanning the full range from 1 to 11 (Figure 3.2), the UMAP visualization suggested a more visible temporal organization. Later visits appeared more concentrated in some regions of the projection, while earlier visits tended to occupy other regions.

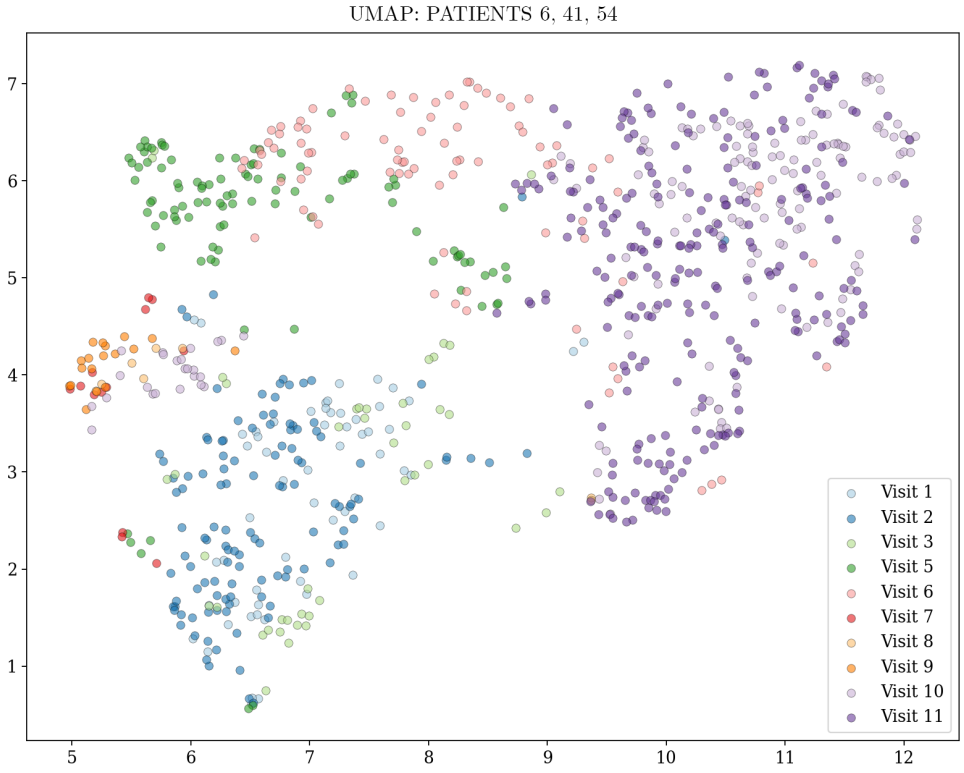

Figure 3.2: Separation of conversation chunks according to visit number. Embedding into a two dimentional space of the patients' P006, P041 and P054 visits: a restricted analisys including only patients with visits spanning the full range from 1 to 11.

Nevertheless, the silhouette score remained close to zero, indicating that the separation was not strong enough to support the use of visit number as a precise categorical label.

The absence of clear temporal clustering motivated the adoption of **supervised learning techniques** capable of identifying specific communication domains within individual dialogue segments.

3.2 Supervised Learning Performance

The supervised learning experiments evaluated whether transformer-based models could identify clinically relevant patient–physician interaction domains after task-specific fine-tuning. In contrast to the unsupervised analysis, supervised models were trained using explicit multi-label annotations provided for the conversation chunks. Two transformer architectures were compared: BioMedBERT and E5-large.

Table 3.1: Per-label test performance by model. Values are reported as mean ± standard deviation across five independent runs with random seeds 42–46.

Model	Accuracy	Precision	Recall	F1
Addressing coping				
BioMedBERT	0.678 ± 0.025	0.498 ± 0.028	0.706 ± 0.033	0.583 ± 0.022
E5-large	0.603 ± 0.159	0.157 ± 0.222	0.323 ± 0.463	0.203 ± 0.279
Addressing symptoms				
BioMedBERT	0.757 ± 0.020	0.677 ± 0.031	0.628 ± 0.055	0.651 ± 0.036
E5-large	0.603 ± 0.142	0.204 ± 0.299	0.317 ± 0.458	0.230 ± 0.317
Discussing cancer treatments				
BioMedBERT	0.712 ± 0.036	0.546 ± 0.049	0.678 ± 0.020	0.604 ± 0.033
E5-large	0.462 ± 0.191	0.291 ± 0.177	0.720 ± 0.438	0.400 ± 0.225
End-of-life planning				
BioMedBERT	0.920 ± 0.016	0.798 ± 0.242	0.292 ± 0.093	0.405 ± 0.090
E5-large	0.744 ± 0.363	0.130 ± 0.241	0.242 ± 0.433	0.095 ± 0.138
Engaging family members				
BioMedBERT	0.548 ± 0.073	0.197 ± 0.013	0.692 ± 0.199	0.303 ± 0.039
E5-large	0.479 ± 0.358	0.093 ± 0.086	0.568 ± 0.522	0.159 ± 0.146
Illness understanding				
BioMedBERT	0.678 ± 0.031	0.566 ± 0.041	0.709 ± 0.050	0.627 ± 0.016
E5-large	0.479 ± 0.133	0.331 ± 0.193	0.746 ± 0.433	0.452 ± 0.254
Relationship and rapport building				
BioMedBERT	0.780 ± 0.031	0.057 ± 0.015	0.533 ± 0.183	0.102 ± 0.027
E5-large	0.364 ± 0.471	0.025 ± 0.018	0.700 ± 0.447	0.046 ± 0.033

Table 3.1 reports the label-wise performance of BioMedBERT and E5-large on the test set. Overall, BioMedBERT achieved higher and more stable performance across all communication domains compared with E5-large.

Performance **varied** across communication domains. Domains characterized by more **explicit** clinical vocabulary, such as *addressing symptoms, treatment discussions*, and *illness understanding*, achieved the **highest predictive accuracy**. Conversely, domains involving more **implicit** relational or interpersonal communication, such as *rapport building* and *family engagement*, proved more **challenging** for automated classification.

As shown in Figure 3.3, among the evaluated labels, the highest F1-scores obtained by BioMedBERT were observed for *addressing symptoms* (0.651 ± 0.036), *illness understanding* (0.627 ± 0.016), *discussing cancer treatments* (0.604 ± 0.033), and *addressing coping* (0.583 ± 0.022).

Moderate performance was observed for *end-of-life planning* (0.405 ± 0.090) and *engaging family members* (0.303 ± 0.039), whereas *relationship and rapport building* showed the lowest F1-score (0.102 ± 0.027).

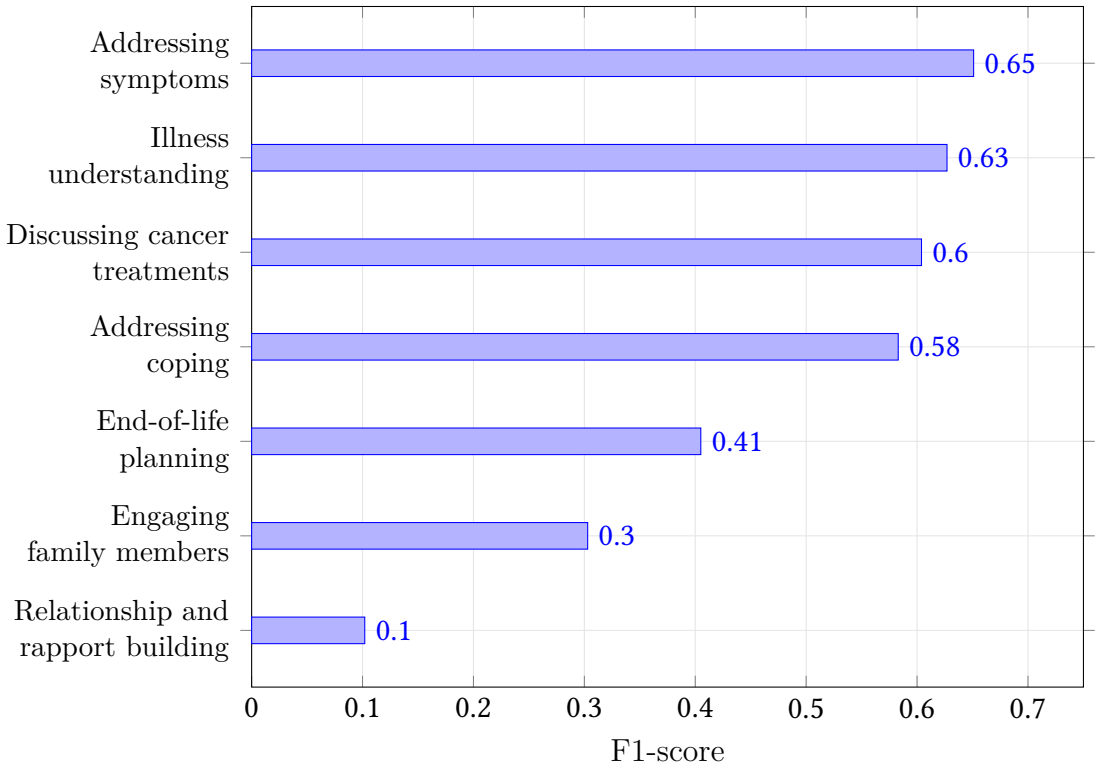

Figure 3.3: BioMedBERT F1-score by communication domain, ordered from highest to lowest performance.

E5-large consistently yielded lower F1-scores across all labels and generally exhibited larger standard deviations, indicating greater variability across runs. The largest differences between the two models were observed for *addressing symptoms*, *addressing coping*, and *relationship and rapport building*, where BioMedBERT substantially outperformed E5-large (Figure 3.4).

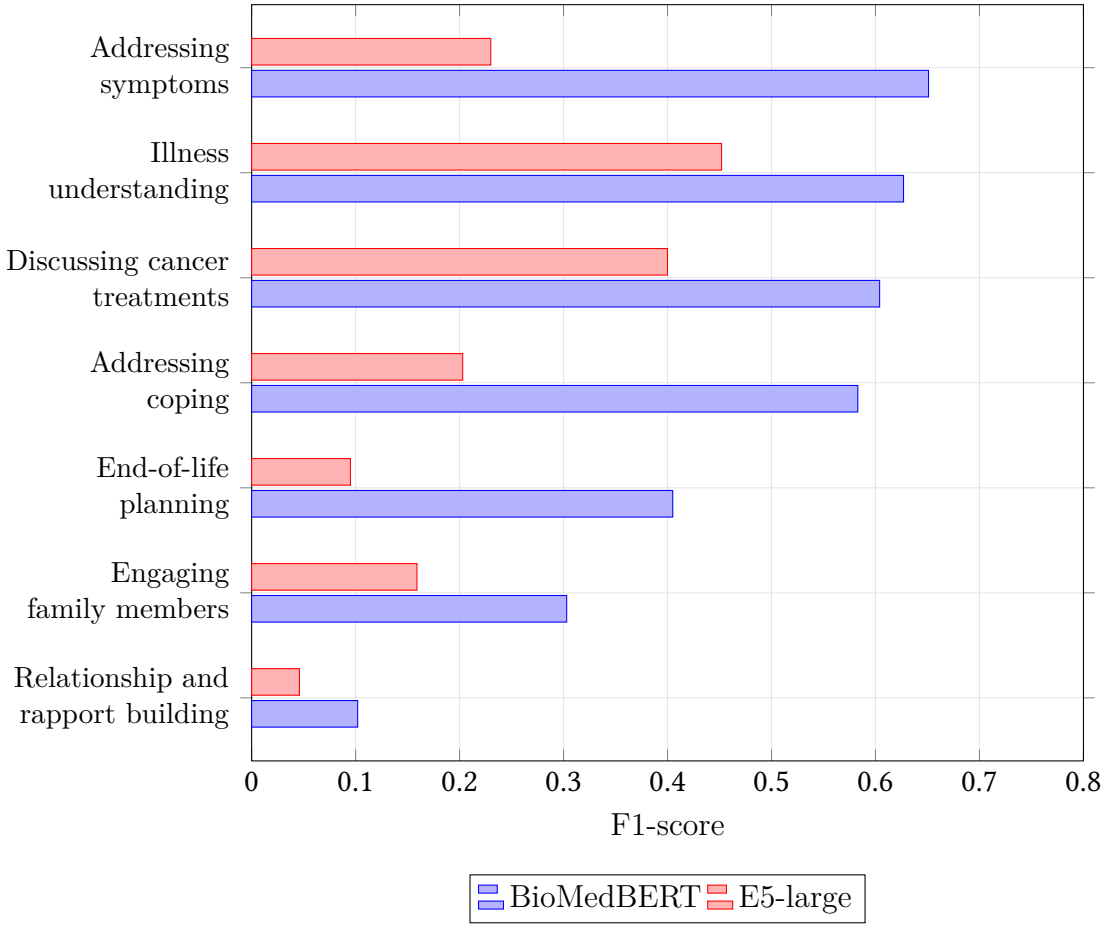

Figure 3.4: Comparison of F1-scores between BioMedBERT and E5-large across communication domains.

BioMedBERT consistently achieved superior performance across nearly all communication domains and was therefore selected for subsequent analyses of the consultation corpus.

Overall, the supervised learning results demonstrate that transformer-based natural language processing models can reliably identify several clinically meaningful communication domains from outpatient ePSC consultations.

In complex clinical natural language processing tasks, where communication domains frequently overlap and class imbalance is common, F1-scores around 0.65 are generally considered indicative of good classification performance.

In the present study, as stated before, the highest performance was achieved for *Addressing symptoms* (F1 = 0.651), followed by *Illness understanding* (F1 = 0.627), *Discussing cancer treatments* (F1 = 0.604), and *Addressing coping* (F1 = 0.583), **demonstrating satisfactory identification of the main communication domains.**

3.3 Temporal Evolution of Communication Domains

To investigate how communication evolves throughout the outpatient ePSC pathway, the BioMedBERT classifier was applied to the segmented consultation corpus. The analysis examined the prevalence of individual communication domains, their temporal evolution across the care trajectory, and the relationships among domains within individual dialogue segments.

As shown in Figure 3.5, across all dialogue segments, **Addressing Coping** was the most prevalent communication domain, (3332/6930, 48.1%), followed by **Engaging Family Members** (3069/6930, 44.3%) and **Illness Understanding** (3015/6930, 43.5%).

End-of-Life Planning was the least frequent communication domain, being identified in 723 of 6930 segments (10.4%).

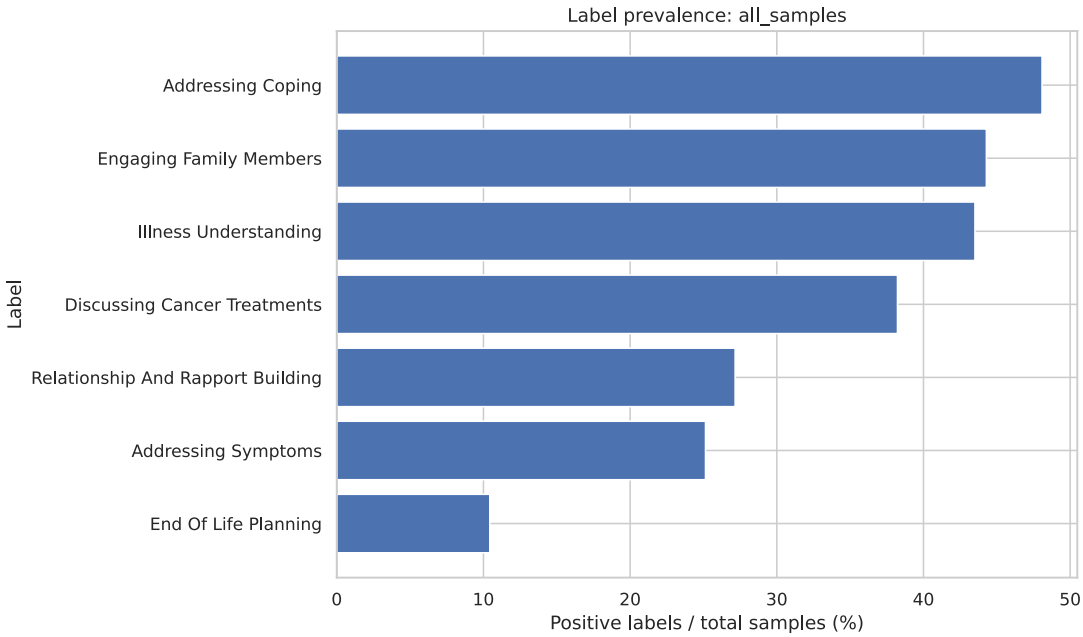

Figure 3.5: Lable Prevalence in all samples

This overall distribution confirms that outpatient ePSC consultations are primarily centered on manage emotional adaptation of patients toghether with family members, while helping them understand the illness and discuss therapeutic decisions.

To characterize temporal changes in communication content, segments from **early visits** (visit number <3) were compared with those from **late visits** (visit number >7).

As shown in Figure 3.6, Figure 3.7 and Figure 3.8 several differences emerged:

- **Relationship and Rapport Building** showed the greatest increase, rising from **14.0%** (140/1000 conversation chunks) in early visits to **35.4%** (792/2239) in late visits, suggesting that the therapeutic relationship became increasingly stong over time.
- **Engaging Family Members** also increased substantially, from **31.7%** (317/1000) to **52.0%** (1164/2239), becoming the most prevalent communication domain during later visits.
- **Addressing Coping** remained essentially unchanged throughout the EPC trajectory, with an identical prevalence of **49.3%** in both early (493/1000) and late (1104/2239) visits.
- **Illness Understanding** showed only a slight reduction, decreasing from **44.2%** (442/1000) in early visits to **42.7%** (957/2239) in late visits.
- **Discussing Cancer Treatments** became less frequent over time, declining from **39.2%** (392/1000) to **35.9%** (804/2239).
- **Addressing Symptoms** demonstrated a marked decrease, falling from **33.2%** (332/1000) in early visits to **18.6%** (416/2239) in later encounters, suggesting that symptom-related discussions became less dominant as the EPC pathway progressed.
- **End-of-life planning**, contrary to what might be expected was more frequent in early visits than in late visits, decreasing from 22.8% in examinations < 3 to 7.7% in examinations > 7.

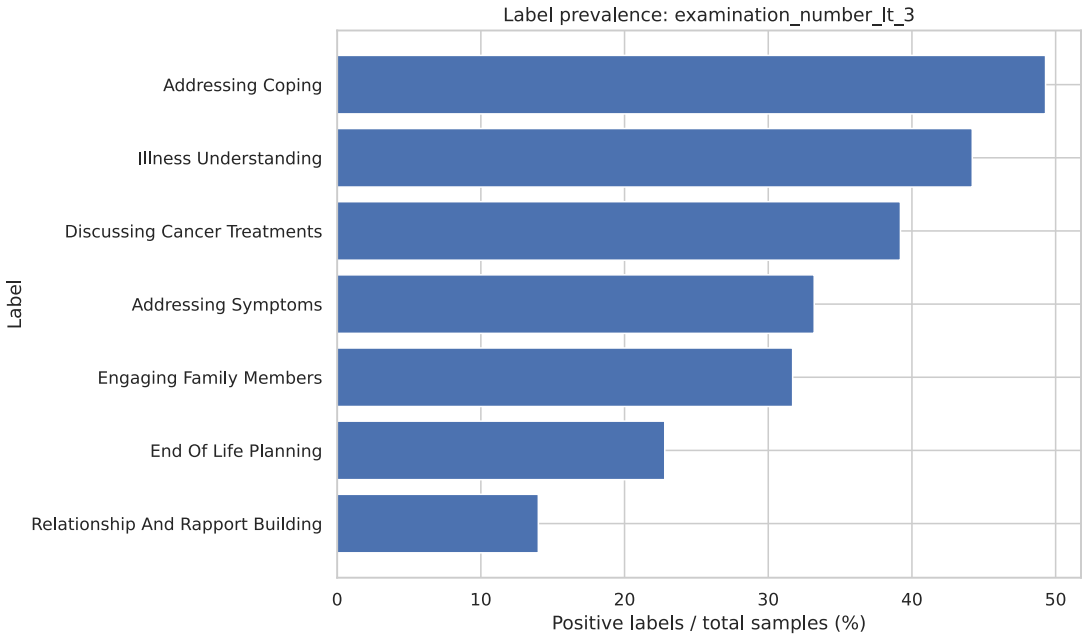

Figure 3.6: Lable Prevalence in Early Visits

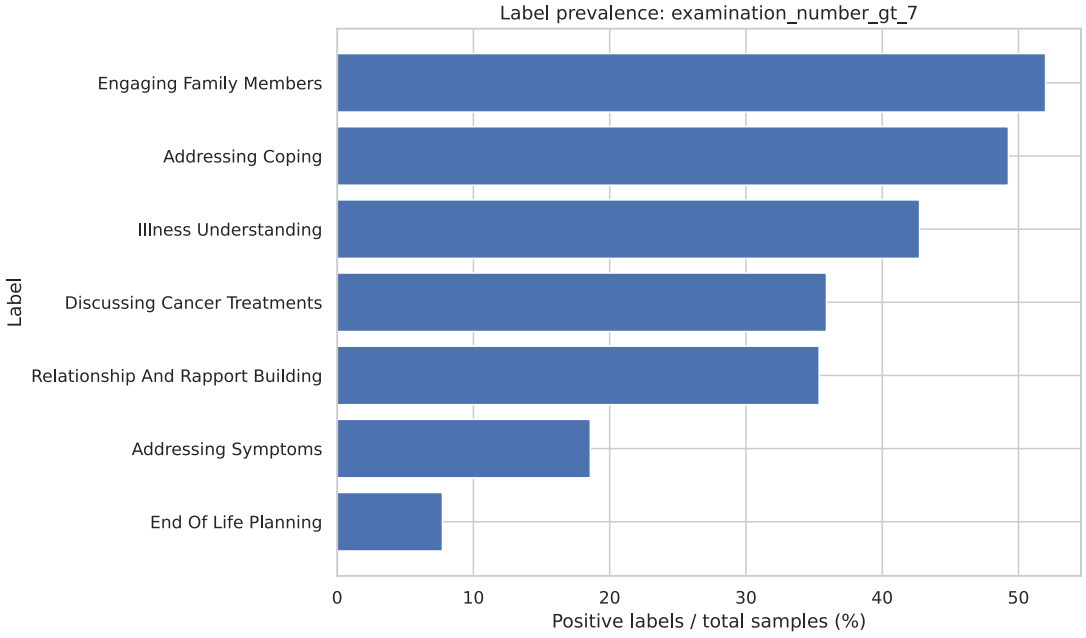

Figure 3.7: Lable Prevalence in Late Visits

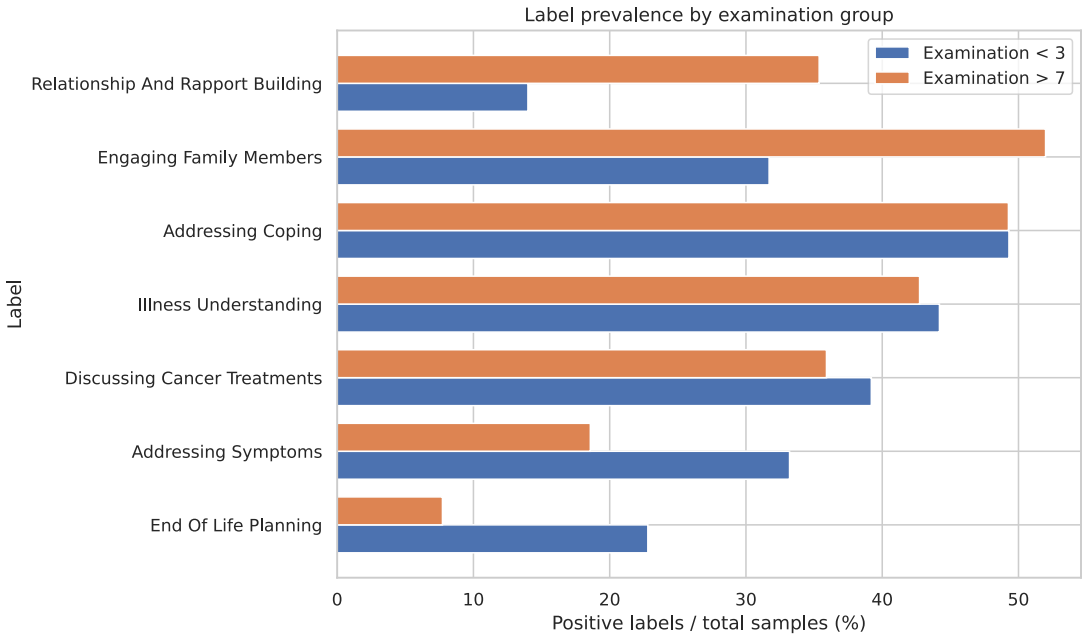

Figure 3.8: Change in label prevalence from early to late examinations

Overall, these findings suggest that communication priorities progressively evolve throughout the ePSC trajectory.

Early consultations predominantly focus on providing coping support for both patients and their family while understanding the disease and discussing treatment options.

Later consultations maintain a strong emphasis on illness understanding and coping, consistent with the fact that hematological malignancies are characterized by continuous evolution and a non-linear disease trajectory that requires continuous assessment, while engaging more and more the family involvment and strenghtening patent-clinician relationship. [16, 28]

The observed reduction in the prevalence of **End-of-Life Planning** during later EPC visits should be interpreted with caution. This communication domain achieved the lowest recall among all labels (0.292 ± 0.093).

Recall represents the proportion of true positive instances that are correctly identified by the classifier; therefore, a low recall indicates that many actual end-of-life discussions are not recognized by the model. Consequently, the apparent decrease in this domain may reflect limitations of the automatic classifier rather than a genuine reduction in end-of-life conversations throughout the EPC trajectory.

3.3.1 Co-occurrency of Communication Domains

Communication domains rarely occurred in isolation.

Most dialogue segments simultaneously contained multiple communication domains, reflecting the multidimensional nature of outpatient palliative care consultations.

Across the entire corpus, the most frequent pairwise co-occurrence involved **Addressing Coping** together with **Engaging Family Members**, followed by the combination of **Illness Understanding** and **Discussing Cancer Treatments** (Figure 3.9).

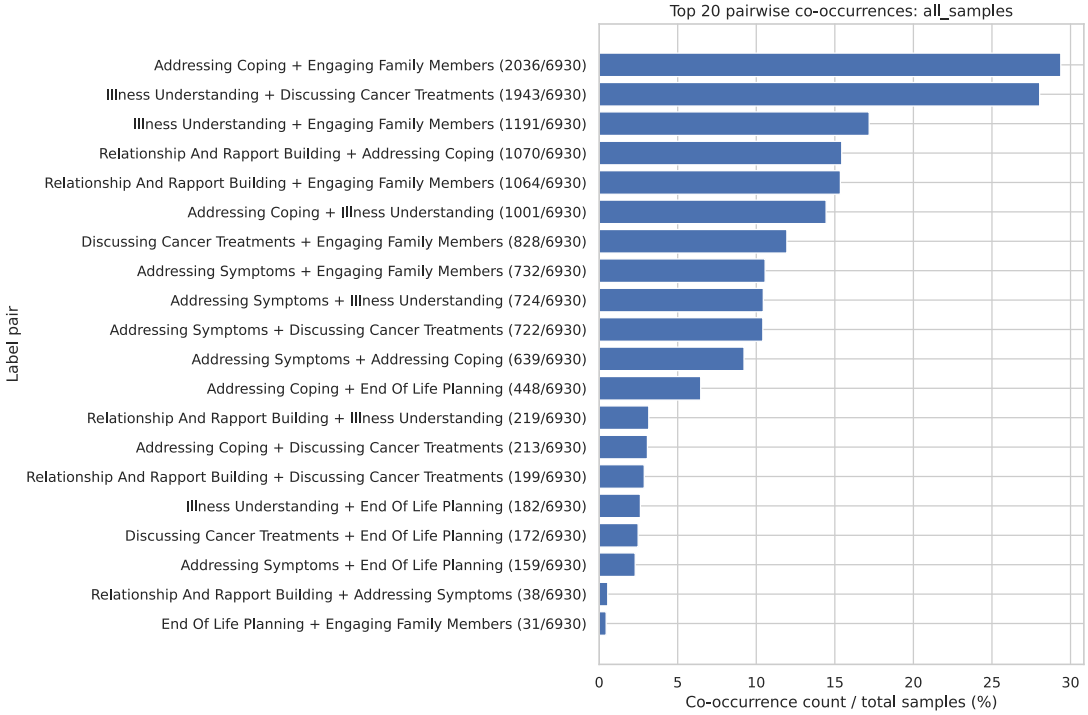

Figure 3.9: Co-occurence of communication domains in all samplesv

These findings indicate that discussions concerning disease understanding are closely integrated with treatment-related conversations, whereas emotional support frequently occurs in the presence of family members.

More importantly, the structure of domain co-occurrences differed between early and late consultations.

During early visits, the most frequent combinations involved the co-occurrence of **Illness Understanding** with **Discussing Cancer treatment**, followed by **Addressing Coping** together with **Engaging Family Members** (Figure 3.10)

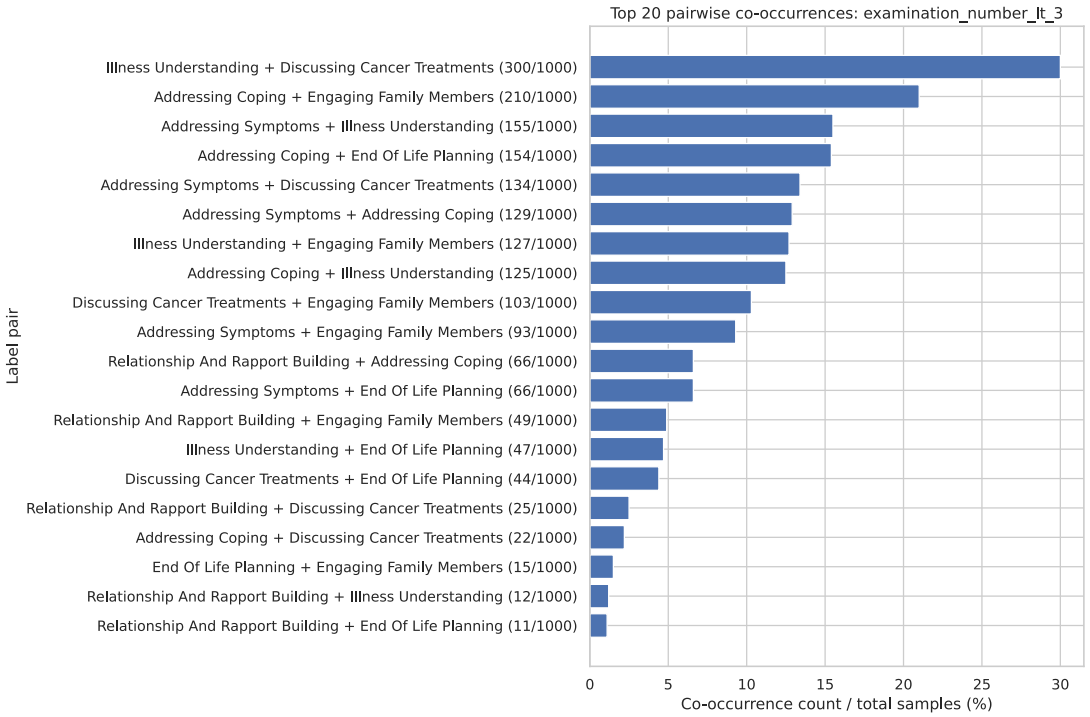

Figure 3.10: Co-occurence of communication domains in Early Visits. Abbreviation: LT, Lower Than.

These findings suggest that the first EPC encounters are characterized by an integrated communication approach in which information sharing, treatment decision-making, and psychosocial support are addressed simultaneously to facilitate patients' adjustment to a newly evolving clinical situation.

Later consultations demonstrated a slightly different conversational structure (Figure 3.11).

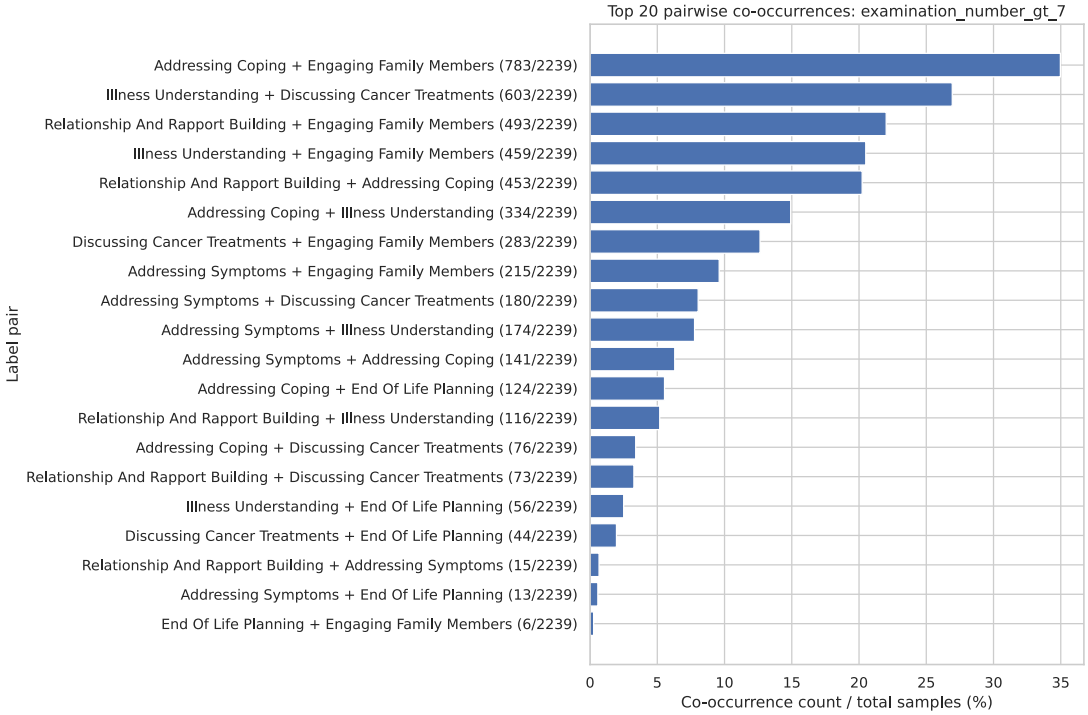

Figure 3.11: Co-occurence of communication domains in Late Visits. Abbreviation: GT, Grater Than.

The dominant co-occurring domains became **Addressing Coping** together with **Engaging Family Members**, highlighting the continued importance of family involvement in supporting patients' emotional adaptation throughout the disease trajectory. This was followed by **Illness Understanding** combined with **Discussing Cancer Treatment**, suggesting that conversations regarding disease status and therapeutic options remained closely interconnected even during later stages of care. Finally, **Relationship and Rapport Building** together with **Engaging Family Members** indicated that later consultations increasingly emphasized maintaining a strong therapeutic alliance while actively involving family members in the ongoing care process.

Taken together, these findings suggest that communication within outpatient EPC evolves from an initial phase primarily focused on helping patients understand their disease, discuss treatment options, and adapt emotionally with the support of family members, toward a more longitudinal model of care centered on maintaining emotional support, strengthening the therapeutic relationship, and continuing shared discussions regarding illness and treatment.

Rather than replacing one communication domain with another, later consultations appear to **build upon** the foundations established during the initial encounters, reflecting the dynamic and adaptive nature of communication in hematological malignancies.

3.4 Relationships Among Communication Domains

Beyond describing the frequency of co-occurent communication domains, we further investigated how these domains were interconnected within outpatient EPC consultations.

To this end, pairwise lift analysis and conditional probability analysis were performed to identify communication domains that co-occurred more frequently than expected by chance and to explore how these relationships evolved across the care trajectory.

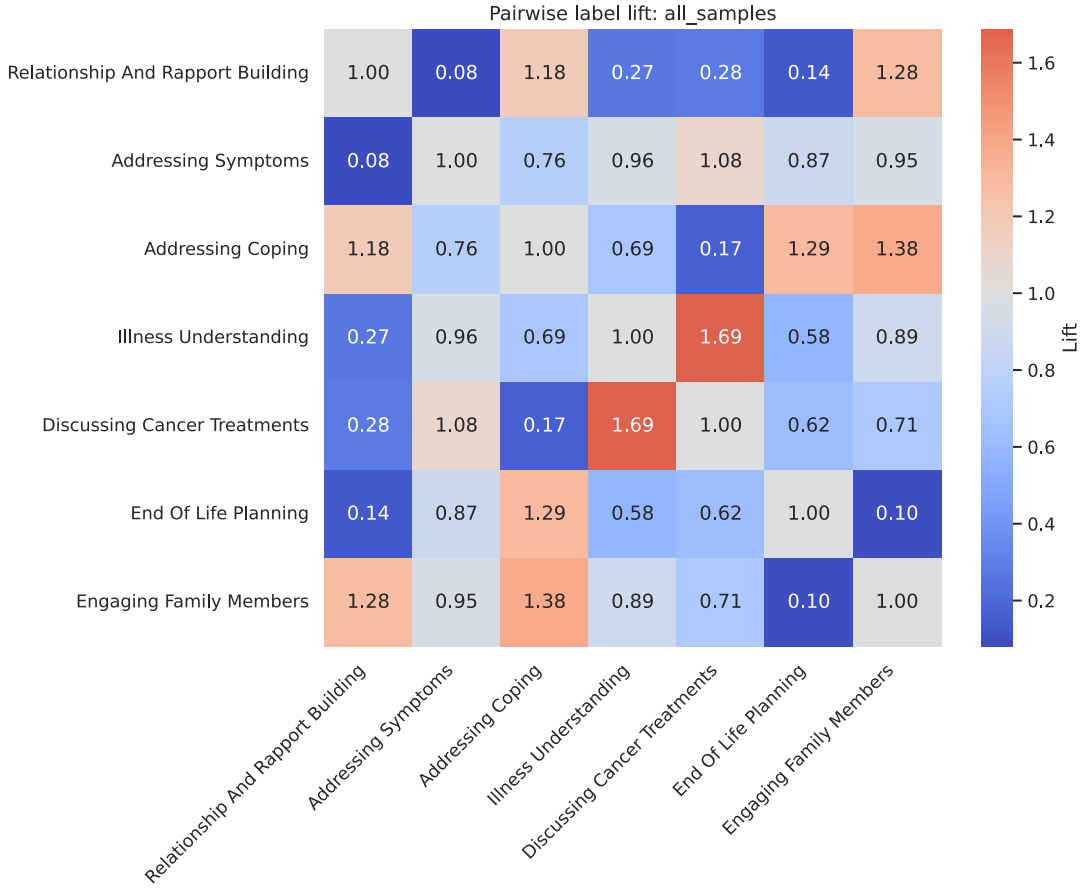

Figure 3.12: Pairwise lift analysis of communication domains across the entire segments' sample. Heatmap showing the pairwise lift values between communication domains.

Lift values greater than 1 indicate that two domains co-occur more frequently than expected by chance, whereas values close to 1 indicate independent occur-

rence. Higher lift values therefore identify communication domains that are more strongly associated within the same dialogue segments.

As shown in Figure 3.2 Across the entire consultation corpus, the strongest positive association was observed between **Illness Understanding** and **Discussing Cancer Treatments**, suggesting that conversations addressing patients' understanding of disease were closely integrated with discussions regarding therapeutic options and treatment decisions

A second consistent association was identified between **Addressing Coping** and **Engaging Family Members**, indicating that these two domains co-occurred substantially more frequently than would be expected based on their individual prevalence alone.

When the analysis was stratified according to visit stage, important differences emerged in the organization of communication domains.

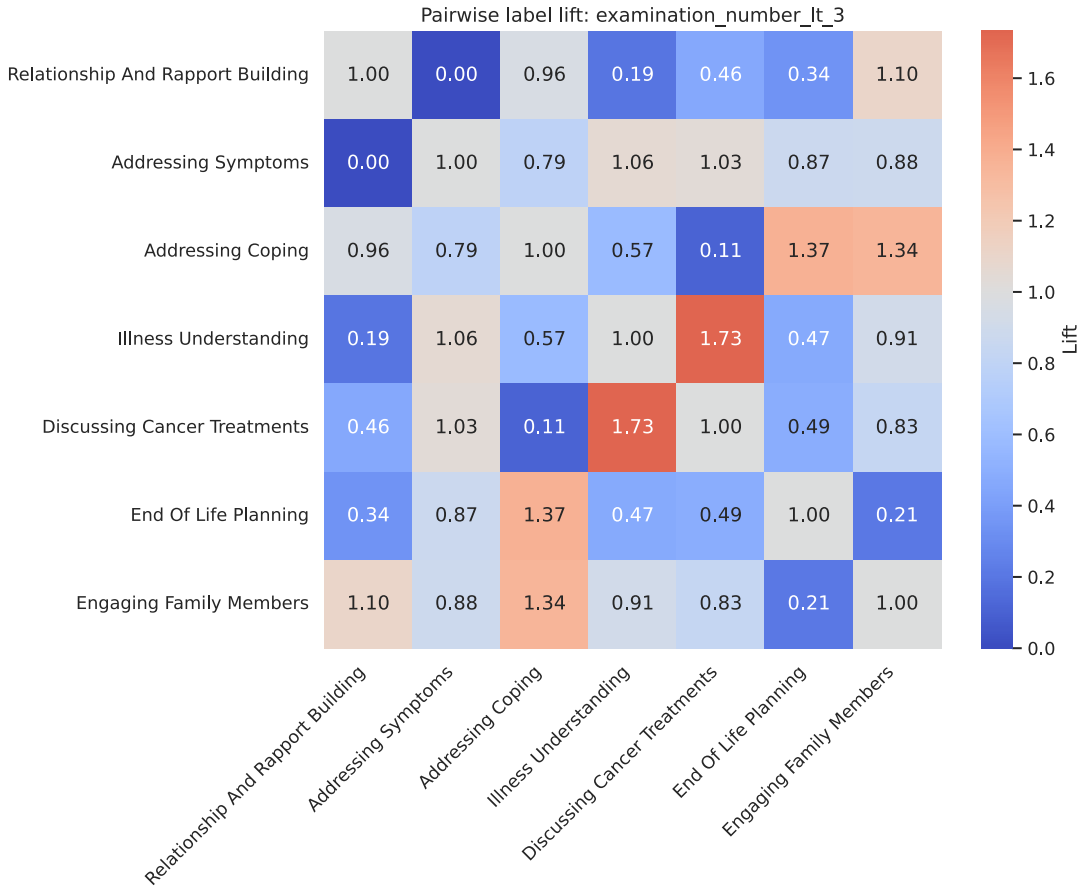

Figure 3.13: Pairwise lift analysis of communication domains during early outpatient EPC consultations (visits < 3).

During the initial phase of the outpatient EPC pathway (Figure 3.13), the prevalence of **Illness Understanding**/**Discussing Cancer Treatments** and **Addressing Coping**/**Engaging Family Members** association was observed also in the eraly visits.

Nevertheless, a new relevant assotiation was observed between **Relationship and Rapport Building** and **Engaging Family Members**.

These findings suggest that family members actively took part of conversations focused on emotional adaptation and contributed to strengthening the therapeutic relationship among all participants, emphasizing the family-centered nature of EPC, in which caregivers are actively involved from the beginning of the care pathway.

Late consultations showed a slightly different pattern of domain associations (Figure 3.14)

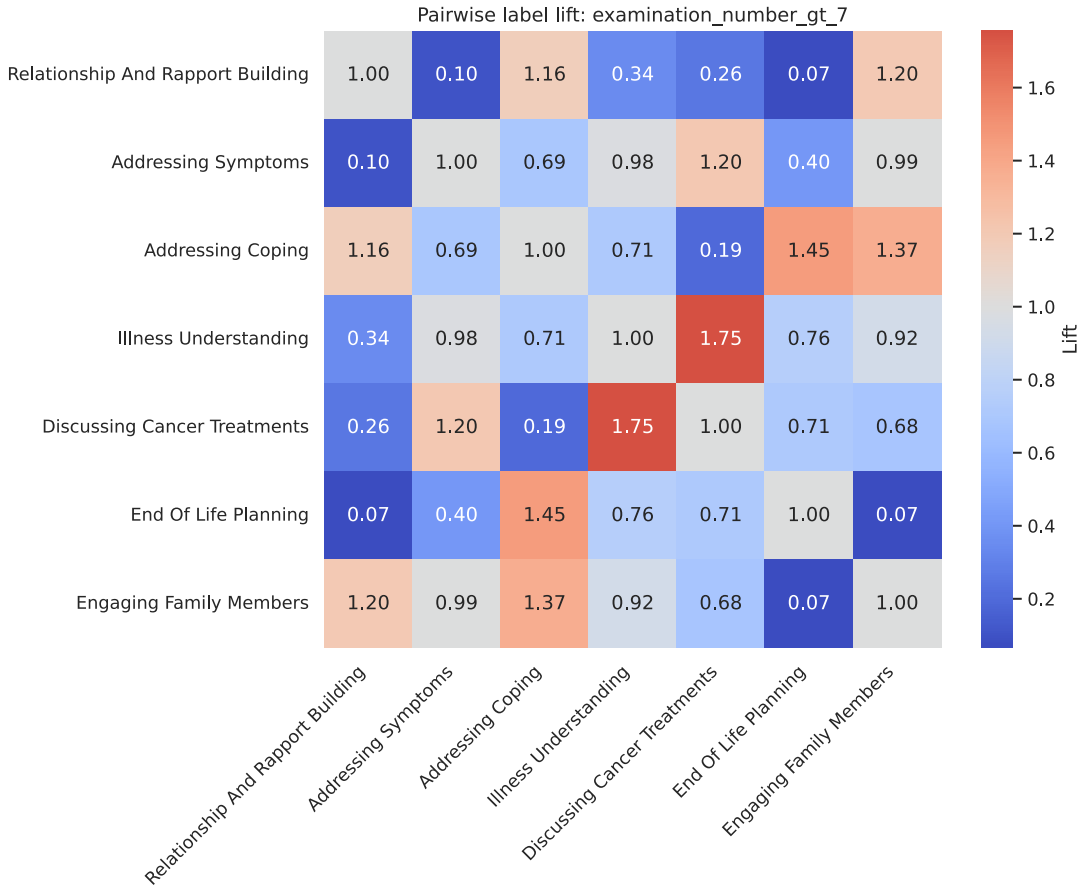

Figure 3.14: Pairwise lift analysis of communication domains during later outpatient EPC consultations (visits > 7).

While maintaining the prevalence of **Illness Understanding**/**Discussing Cancer Treatments** and **Addressing Coping**/**Engaging Family Members** association, **Relationship and Rapport Building** and **Engaging Family Members** became more prevalent.

New associtions emerged, such as the association between **Addressing Symptoms** and **Discussing Cancer Treatments**, and between **Relationship and Rapport Building** and **Addressing Coping**.

Overall, these findings suggest that communication during later ePSC consultations became more integrated and relationship-oriented.

While the core associations between **Illness Understanding** and **Discussing Cancer Treatments**, as well as between **Addressing Coping** and **Engaging Family Members**, remained stable over time, the increasing prevalence of the association between **Relationship and Rapport Building** and **Engaging Family Members** indicates a growing emphasis on strengthening the therapeutic alliance while actively involving caregivers.

In addition, the emergence of new associations linking **Addressing Symptoms** with **Discussing Cancer Treatments** and **Relationship and Rapport Building** with **Addressing Coping** suggests that communication became progressively more holistic, integrating symptom management, emotional support, clinical decision-making, and relationship building within the same conversations.

Associations involving **End-of-Life Planning** were excluded from this interpretation, as they should be considered cautiously because, as reported the beginning of this analysis, the classifier showed the lowest recall for this domain, reducing confidence in estimates of its temporal relationships with other communication domains.

To further characterize these communication patterns, conditional probability analysis was performed (Figure 3.15).

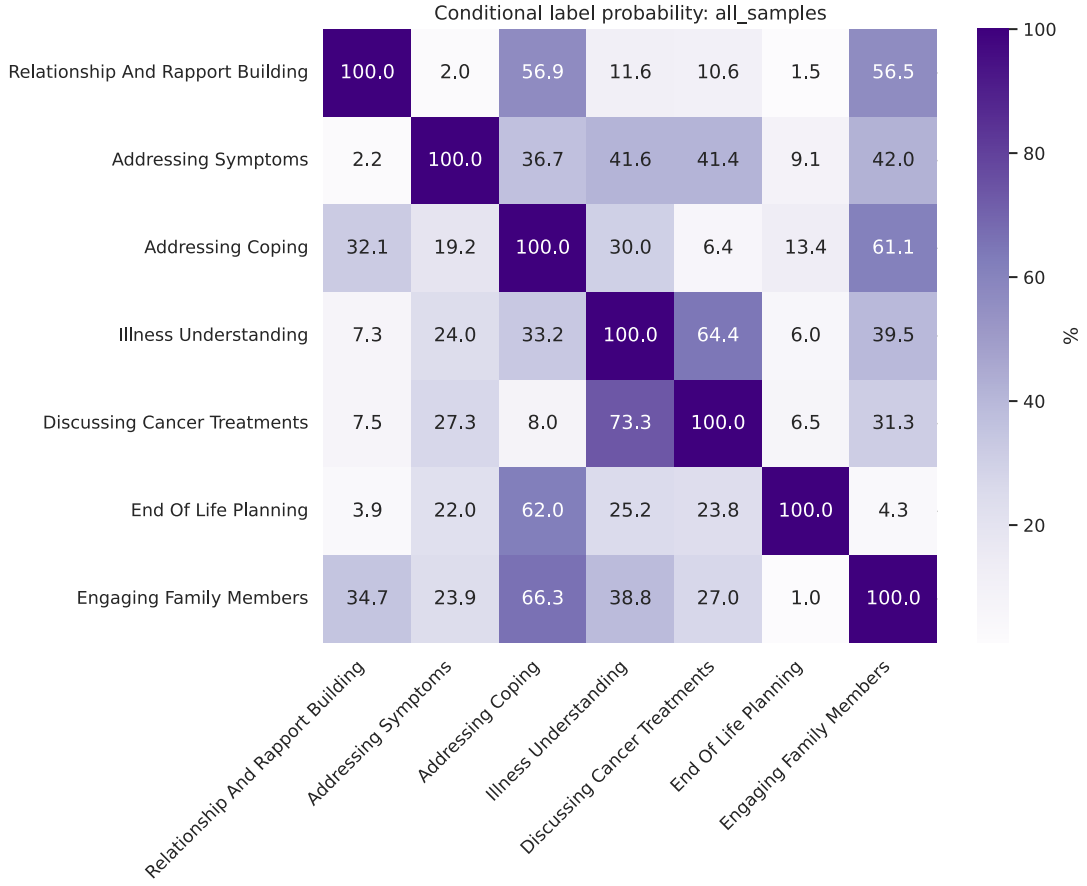

Figure 3.15: Conditional probability of communication domain co-occurrence across the entire outpatient EPC segments' sample. Heatmap showing the conditional probability that a communication domain (column) is present given the occurrence of another domain (row).

The strongest conditional relationship was observed between **Discussing Cancer Treatments** and **Illness Understanding**, with the presence of **Discussing Cancer Treatments** increasing the probability of co-occurring **Illness Understanding** to 73.3%. Conversely, the presence of **Illness Understanding** increased the probability of **Discussing Cancer Treatments** to 64.4%.

Together, these findings indicate that discussions regarding therapeutic options were rarely conducted in isolation but were typically embedded within broader conversations aimed at improving patients' understanding of their disease, prognosis, and treatment pathway.

The presence of **Engaging Family Members** increased the probability that conversations also addressed **Addressing Coping** (66.3%), while the presence of **Addressing Coping** increased the probability of co-occurring **Engaging Family Members** (61.1%).

This bidirectional relationship highlights the close integration between emotional support and family involvement, suggesting that caregivers actively participated in helping patients adapt psychologically to their illness and that coping-related discussions frequently occurred within a family-centered context.

Although the presence of **End-of-Life Planning** increased the probability of co-occurring **Addressing Coping** (62.0%), this finding should not be overinterpreted given the limited performance of the classifier in identifying the **End-of-Life Planning** domain.

Overall, conditional probability analyses demonstrated that the occurrence of one communication domain substantially increased the likelihood of other related domains being discussed within the same dialogue segment, supporting the view that outpatient ePSC communication is organized as an interconnected network of complementary communication tasks rather than as a series of isolated topics.

This network-based perspective provides a more comprehensive representation of outpatient ePSC communication than analyses based solely on the frequency of individual topics and highlights the dynamic nature of communication throughout the disease trajectory.

Interestingly, these segment-based findings closely reproduce the trajectory-adaptive communication model previously identified through retrospective analysis of electronic medical records in the same outpatient ePSC program. [36]

The convergence of findings obtained through two independent methodological approaches: clinical documentation and direct transcript analysis, supports the robustness of the proposed communication model and suggests that the observed temporal evolution reflects genuine clinical communication rather than documentation practices.

Chapter 4

Discussion

To our knowledge, this is one of the first studies to apply transformer-based natural language processing (NLP) techniques to the analysis of prospectively collected outpatient early palliative supportive care (ePSC) consultations in patients with hematological malignancies. By combining manual annotation with supervised machine learning, this study characterized the core communication domains delivered during routine clinical encounters and explored how these domains evolve and interact throughout the ePSC trajectory.

Overall, the findings support the concept that ePSC is a dynamic and multidimensional intervention. Rather than consisting of isolated communication tasks, outpatient consultations addressed multiple complementary domains simultaneously, including illness understanding, treatment discussions, coping support, symptom management, relationship building, and family engagement. These observations are consistent with the conceptual models proposed by Jacobsen, Yoong, and Hoerger, who identified these domains as the core components of early palliative care interventions [14, 17, 18].

However, the present study extends previous work by demonstrating that these domains form an interconnected communication network whose organization changes throughout the disease trajectory.

The unsupervised analysis showed limited separation of consultation content according to visit number. Rather than representing a methodological limitation, this finding is clinically plausible. Hematological malignancies are characterized by heterogeneous and non-linear disease trajectories, with repeated transitions between active treatment, remission, relapse, and supportive care. Consequently, patients at the same visit number may face very different clinical situations, requiring different communication priorities.

This observation supports the trajectory-adaptive model of ePSC previously proposed in hematology, according to which communication evolves according to patients' changing clinical and psychosocial needs rather than following a predefined chronological sequence [16, 28, 36].

The supervised analyses demonstrated that transformer-based models can successfully identify several clinically meaningful communication domains. BioMedBERT consistently outperformed the embedding-based E5-large model, particularly for domains characterized by explicit biomedical language, such as **symptom management**, **illness understanding**, **treatment discussions**, and **coping support**.

Conversely, relational domains, including **rapport building** and **family engagement**, proved more difficult to classify automatically, likely because they rely on contextual and interpersonal features rather than specific medical terminology.

Importantly, the limited recall achieved for **End-of-Life Planning** suggests that findings involving this domain should be interpreted cautiously, as a proportion of true end-of-life discussions may not have been recognized by the classifier.

Beyond demonstrating the feasibility of automated communication analysis, the supervised approach allowed a comprehensive characterization of consultation content.

Illness understanding, **coping support**, and **treatment discussions** emerged as the most prevalent communication domains, confirming that outpatient ePSC extends well beyond symptom control and addresses patients' informational and psychological needs throughout the disease trajectory.

Moreover, comparisons between early and later consultations suggested that communication priorities progressively reorganize according to patients' evolving circumstances while maintaining **illness understanding** and **coping support** as central elements of the intervention.

One of the most relevant findings of the present study concerns the relationships between communication domains. Co-occurrence, conditional probability, and pairwise lift analyses consistently demonstrated that communication domains rarely occurred in isolation.

Instead, **discussions about treatment** were closely integrated with **illness understanding**, whereas **coping support** was strongly associated with **family involvement**. These observations reinforce the holistic philosophy of palliative care, in which physical, psychological, informational, and relational aspects are addressed simultaneously within the same clinical encounter rather than through separate conversations.

These findings are particularly relevant in hematological malignancies. Compared with many solid tumors, hematological diseases are characterized by persistent prognostic uncertainty, rapidly evolving therapeutic strategies, and repeated changes in goals of care [13, 16, 28].

The persistence of **illness understanding** and **coping support** throughout the trajectory therefore appears clinically coherent, reflecting the continuous need to revisit information, support adaptation, and facilitate shared decision-making as patients' clinical conditions evolve.

From a methodological perspective, this study also highlights the potential contribution of artificial intelligence to palliative care research. While manual annotation remains essential for developing reliable training datasets, transformer-based models offer the opportunity to analyze large collections of clinical conversations objectively and reproducibly. Such approaches may facilitate communication audits, quality improvement initiatives, and future studies investigating the relationship between specific communication patterns and patient-reported outcomes.

In conclusion, the present findings support the view that outpatient ePSC should be considered an adaptive communication process rather than a standardized intervention. By combining artificial intelligence with clinically grounded communication frameworks, this study provides a novel methodological approach for investigating how early palliative care is delivered in real-world hematology practice.

Future studies integrating transcript-based communication analyses with patient-reported outcomes will be essential to identify which communication patterns are most strongly associated with improved patient-centered outcomes and to support the development of increasingly personalized models of early palliative supportive care.

Chapter 5

Study Limitations

This study has several limitations that should be considered when interpreting the results.

- First, this was a **single-center study** conducted within the ePSC clinic of the section of Hematology, Azienda Ospedaliero-Universitaria (AOU) Policlinico, university of Modena and Reggio Emilia, Modena. Therefore, the findings may reflect the specific organization, clinical practice, and communication style of this center.

  The structure of the visits, the expertise of the clinicians involved, and the local model of integration between hematology and palliative care may have influenced the content of the consultations, even though ePSC interventions were delivered following ASCO guidelines [41] and the communication domains have been well established in literature and consistently identified across different studies and clinical settings [14, 17, 36].

  Although the single-center design may limit the external validity of the findings, it is important to note that one of the ultimate goals of this research is precisely to evaluate whether the model developed in Modena can be replicated and implemented in other institutions. By systematically identifying and characterizing the core components of the intervention, the present study aims to provide the **foundations** for the development of a **standardized** and **reproducible** model of early palliative supportive care that could be adopted on a larger scale across different hematology centers.

- Second, the sample size was **relatively limited**. Although the dataset included a large number of conversation chunks, these chunks were derived from a smaller number of patients. Consequently, several chunks originated

from the same individual and may therefore share similar clinical histories, linguistic patterns, and relational dynamics with the physician.

However, the study cohort included patients with **different hematological malignancies**, including acute myeloid leukemia, lymphoma, and multiple myeloma, thus increasing the **clinical heterogeneity** of the sample.

Furthermore, whenever possible, **multiple consultations** from the same patient were intentionally included in order to capture different stages of the ePSC trajectory and to investigate the longitudinal evolution of communication domains over time.

While this approach does not completely eliminate the risk of patient-level dependency, it allowed the analysis to better represent the dynamic and adaptive nature of ePSC consultations.

- Third, although the annotation scheme was based on communication domains previously described in the literature, the annotation process remains **partly subjective**.

  Future studies should include multiple independent annotators and assess inter-rater agreement to further improve annotation reliability.

  However, this limitation is partially attenuated by the fact that the annotation was performed according to established frameworks from the ePSC literature and on a large dataset comprising more than 8,000 conversation chunks.

  The annotated subset was specifically designed to provide clinically meaningful labels while ensuring the feasibility of the project.

- Fourth, the transcripts were translated from Italian into English before being processed by English-language NLP models. This approach allowed the use of well-established transformer-based models, but translation may have altered subtle linguistic, emotional, or cultural aspects of the original conversations. Some expressions related to suffering, coping, hope, or awareness of illness may not have an exact equivalent across languages.

  Therefore, future work should consider the use of Italian-language or multilingual clinical models.

- Fifth, the supervised models were developed on a limited annotated dataset. This may affect model generalizability and increase the risk of overfitting. Although patient-level splitting was considered to reduce information leakage, larger datasets will be needed to train and validate more robust models. External validation on independent transcripts from other institutions will be essential before these methods can be considered for broader research or clinical use.

- Sixth, transcript-level analyses accumulated prediction errors across dialogue segments, resulting in a higher number of false-positive classifications than segment-level analyses. Consequently, segment-level analyses were considered the primary analytical framework, whereas transcript-level findings should be regarded as exploratory.

Chapter 6

Study Strengths

In addition to the limitations discussed above, the present study is characterized by several notable strengths.

- First, to the best of our knowledge, this is one of the first studies to apply **artificial intelligence** and **natural language processing techniques** to the analysis of prospectively collected early palliative supportive care (ePSC) consultations in patients with hematological malignancies. While previous studies have investigated the content of ePSC encounters using qualitative methodologies, the use of computational approaches offers the possibility of systematically analyzing large volumes of clinical communication and generating reproducible quantitative insights.
- Second, the study was based on **real-world clinical encounters** collected within an established outpatient ePSC program. Consequently, the analyzed conversations reflect routine clinical practice rather than interactions occurring in an experimental setting. This increases the ecological validity of the findings and provides a realistic representation of communication processes occurring during ePSC consultations.
- Third, unlike many previous studies that focused on single consultations or specific phases of the disease trajectory, the present dataset included consultations from different stages of follow-up. Multiple transcripts were available for many patients, allowing the analysis to capture the **longitudinal evolution of communication domains** throughout the ePSC trajectory. This aspect is particularly relevant given the dynamic and adaptive nature of palliative care interventions, whose content is known to change according to patients' evolving clinical and psychosocial needs [14, 17, 36].

- Fourth, the annotation framework was grounded in previously published models of early palliative care communication. The selected domains were derived from well-established conceptual frameworks developed in both solid and hematological malignancies [14, 17, 36]. This approach enhances the **clinical relevance of the annotation process** and facilitates comparison with previous studies.

- Fifth, in the unsupervised results visit number was used as an **approximate indicator** of the patient journey.

  This underlined how visit chronology does not necessarily correspond to a specific clinical stage. In hematological malignancies, disease trajectories are often non-linear and unpredictable: an early visit may already include discussions about prognosis or end-of-life preferences, whereas a later visit may focus mainly on routine symptom management. Therefore, visit number resulted to be a weak ordinal proxy rather than as a precise marker of disease progression or care needs.

  Although this finding may initially appear as a methodological challenge, it also highlights how each consultation can provide relevant information regardless of its chronological position within the care pathway. This characteristic allowed the dataset to capture a broad spectrum of communication domains and reflects the real-world complexity of ePSC consultations.

- Sixth, the convergence between findings obtained through manual annotation, NLP analyses, and our previous electronic medical record study substantially strengthens the validity of the proposed trajectory-adaptive communication model. [36]

  Finally, beyond its immediate findings, the study establishes a methodological framework that can be expanded in future investigations.

  By identifying clinically meaningful communication domains and developing automated approaches for their recognition, this work represents a first step toward the large-scale evaluation of ePSC delivery. Such approaches may ultimately contribute to the standardization, dissemination, and implementation of effective integrated palliative care models across different hematology centers.

Chapter 7

Future Direction

In the present study, as an exploratory analysis, the trained classifier was also applied at the transcript level across the complete consultation corpus. Although transcript-level classification was more susceptible to false-positive accumulation, owing to the propagation of segment-level prediction errors, the overall temporal trends mirrored those observed in the segment-based analyses.

A potential direction for future research would be to extend the present segment-based analysis to the transcript level, by improving the performance of the classifier, allowing communication patterns to be examined across entire consultations rather than individual conversation segments.

Another important step forward will be to investigate the relationship between the content of EPC consultations and patient-reported outcomes (PROs), in order to identify which communication domains and communication patterns are most strongly associated with quality of life, symptom burden, psychological distress, coping, end-of-life awareness and overall clinical benefit for patients.

Chapter 8

Conclusions

Early palliative supportive care has progressively evolved from a symptom-oriented intervention to a comprehensive model of care addressing the physical, psychological, informational, and relational needs of patients with hematological malignancies throughout the disease trajectory.

The results of this study further support this concept by demonstrating that, rather than occurring as isolated communication tasks, the core components of outpatient early palliative supportive care form **dynamic communication networks** whose organization progressively adapts to patients' evolving clinical, informational, and emotional needs.

The application of transformer-based natural language processing enabled the systematic characterization of communication domains within real-world outpatient consultations, demonstrating the feasibility of combining artificial intelligence with clinically grounded communication frameworks.

In addition to confirming the multidimensional nature of EPC, this approach provides a scalable and reproducible methodology for studying complex clinical conversations and their evolution over time.

Future studies integrating transcript-based communication analyses with patient-reported outcomes and multicenter validation will be essential to identify which communication patterns are most strongly associated with improved patient-centered outcomes. Ultimately, these findings may contribute to a deeper understanding of the mechanisms underlying the effectiveness of early palliative supportive care and support the development of increasingly standardized, evidence-based, and personalized models of integrated care for patients with hematological malignancies.

Appendix A

Supplementary Tables

Table A.1: Characteristics of the analyzed transcript dataset

Variable	**Value**
Patients included	48
Recorded consultations	128
Conversation chunks	8293
Annotated chunks	1084
Annotated proportion	15.9%
Consultations per patient, mean ± SD	2.7 ± 1.5
Consultations per patient, median (IQR)	3 (1–4)
Range of consultations per patient	1–6
Chunk size	10 utterances

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Questo percorso mi ha insegnato che la medicina non è fatta soltanto di diagnosi e trattamenti, ma soprattutto di ascolto, presenza e attenzione verso la persona.

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Bibliography

[1] Ferrara F, Schier CA. Acute myeloid leukaemia in adults. Lancet Lond Engl. 2013;381(9865):484-495. DOI:10.1016/S0140-6736(12)61727-9

[2] Heuser M, Ofran Y, Boissel N, et al. Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31(6):697-712. DOI:10.1016/j.annonc.2020.02.018

[3] Pelcovits A, Niroula R. Acute Myeloid Leukemia: A Review. R I Med J (2013). 2020 Apr 1;103(3):38-40. PMID: 32236160

[4] Hussain M, Yellapragada S, Al Hadidi S. Differential Diagnosis and Therapeutic Advances in Multiple Myeloma: A Review Article. Blood Lymphat Cancer. 2023 Sep 15;13:33-57. doi: 10.2147/BLCTT.S272703. PMID: 37731771; PMCID: PMC10508231

[5] Dimopoulos, M.A., Terpos, E., Boccadoro, M. et al. EHAEMN Evidence-Based Guidelines for diagnosis, treatment and follow-up of patients with multiple myeloma. Nat Rev Clin Oncol 22, 680700 (2025). https://doi.org/10.1038/s41571-025-01041-x

[6] Francesca Fazio, Martina Gherardini, Elena Rossi. Long-Term Survival with Multiple Myeloma: An Italian Experience. Cancers 2025, 17(3), 354; https://doi.org/10.3390/cancers17030354

[7] Shi, Y., Cao, T., Xu, Y. et al. Global, regional, and national burden of lymphoma from 1990 to 2021: a comprehensive analysis based on the global burden of disease study 19902021. Eur J Med Res 31, 338 (2026). https://doi.org/10.1186/s40001-025-03832-5

[8] Armitage J. Long-term toxicity of the treatment of Hodgkins disease, Annals of Oncology, 9, s133-s136

[9] Chong EA, Tomasulo EB, Barta SK. 2026 Update on the Management of Diffuse Large B-Cell Lymphoma. Am J Hematol. 2026 Apr;101(4):832-863. doi: 10.1002/ajh.70229. Epub 2026 Feb 7. PMID: 41654318; PMCID: PMC12994129.

[10] Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363(8):733-742. doi:10.1056/NEJMoa1000678

[11] Potenza L, Scaravaglio M, Fortuna D, et al. Early palliative/supportive care in acute myeloid leukaemia allows low aggression end-of-life interventions: observational outpatient study. BMJ Support Palliat Care. Published online November 8, 2021: bmjspcare-2021-97002898. doi:10.1136/bmjspcare-2021-002898

[12] Bandieri E, Banchelli F, Artioli F, et al. Early versus delayed palliative/supportive care in advanced cancer: an observational study. BMJ Support Palliat Care. 2020;10(4):e32-e32. doi:10.1136/bmjspcare-2019-001794

[13] Niscola P, Piccioni D, Giovannini M. Palliative care interventions and their early integration in the management of older adults with acute myeloid leukemia: a narrative review. Ann Palliat Med. 2025 Jul;14(4):393-411. doi: 10.21037/apm-25-32. PMID: 40769734.

[14] Yoong J, Park ER, Greer JA, et al. Early Palliative Care in Advanced Lung Cancer: A Qualitative Study. JAMA Intern Med. 2013;173(4):283. doi:10.1001/jamainternmed.2013.1874

[15] Zimmermann C, Ryan S, Hannon B, et al. Team-based outpatient early palliative care: a complex cancer intervention. BMJ Support Palliat Care. Published online August 12, 2019:bmjspcare-2019-001903. doi:10.1136/bmjspcare-2019-001903

[16] Potenza L, Luppi M, Zimmermann C, Bandieri E. Early palliative care in haematological malignancies. BMJ Support Palliat Care. Published online February 22, 2024:spcare-2024-004812. doi:10.1136/spcare-2024-004812

[17] Hoerger M, Greer JA, Jackson VA, et al. Defining the Elements of Early Palliative Care That Are Associated With Patient-Reported Outcomes and the Delivery of End-of-Life Care. J Clin Oncol. 2018;36(11):1096-1102. doi:10.1200/JCO.2017.75.6676

[18] Jacobsen J, Jackson V, Dahlin C, Greer J, Perez-Cruz P, Billings JA, Pirl W, Temel J. Components of early outpatient palliative care consultation in patients with metastatic nonsmall cell lung cancer. J Palliat Med. 2011 Apr;14(4):459-64. doi: 10.1089/jpm.2010.0382. Epub 2011 Mar 18. PMID: 21417739.

[19] Steinhauser KE, Alexander SC, Byock IR, George LK, Olsen MK, Tulsky JA: Do preparation and life completion discussions improve functioning and quality of life in seriously ill patients? pilot randomized control trial. J Palliat Med 2008;11:12341240.

[20] Ballan-Haj, M., Midlej, K., Silverman, B. et al. Assessing the correlation between patient and family reported outcome measures and multiple myeloma clinical parameters. Sci Rep 15, 45172 (2025). https://doi.org/10.1038/s41598-025-28967-7

[21] Invernizzi R. Images from the Haematologica Atlas of Hematologic Cytology: plasma cell myeloma. Haematologica 2021; 106(4):925-925; https://doi.org/10.3324/haematol.2021.278331.

[22] J Oral Maxillofac Pathol 2010 Jul-Dec;14(2):7376. doi: 10.4103/0973-029X.72506

[23] Hodgkin's lymphoma histology image. *Wikipedia*. Accessed `https://en.wikipedia.org/wiki/Hodgkin_lymphoma`

[24] Acute myeloid leukemia bone marrow aspirate. *Wikipedia*. Accessed `https://en.wikipedia.org/wiki/Acute_myeloid_leukemia`

[25] Tesio L, et al. Patient-reported outcomes and psycho-oncological screening in hematology: a practical example of routine electronic monitoring. Supportive Care in Cancer. 2020; https://doi.org/10.1007/s12254-020-00628-7

[26] El-ň Jawahri A, LeBlanc TW , Kavanaugh A, et al. Effectiveness of integrated palliative and oncology care for patients with acute myeloid leukemia. JAMA Oncol 2021;7:23845

[27] Cheng H- WB, Li C-W , Chan K-Y, et al. End- Of- Life characteristics and palliative care provision for elderly patients suffering from acute myeloid leukemia. Support Care Cancer 2015;23:1116

[28] Shaulov A, Aviv A, Alcalde J, Zimmermann C. Early integration of palliative care for patients with haematological malignancies. Br J Haematol. 2022 Oct;199(1):14-30. doi: 10.1111/bjh.18286. Epub 2022 Jun 7. PMID: 35670630; PMCID: PMC9796711.

[29] Potenza L, Scaravaglio M, Fortuna D, et al. Early palliative/supportive care in acute myeloid leukaemia allows low aggression end-of-life interventions: observational outpatient study. BMJ Support Palliat Care. Published online November 8, 2021:bmjspcare-2021- 97 002898. doi:10.1136/bmjspcare-2021-002898

[30] Jacob Devlin, Ming-Wei Chang, Kenton Lee, and Kristina Toutanova. BERT: Pre-training of Deep Bidirectional Transformers for Language Understanding. In North American Chap- ter of the Association for Computational Linguistics, 2019.

[31] Edward J Hu, yelong shen, Phillip Wallis, Zeyuan Allen-Zhu, Yuanzhi Li, Shean Wang, Lu Wang, and Weizhu Chen. LoRA: Low-Rank Adaptation of Large Language Models. In International Conference on Learning Representations, 2022.

[32] rene Li, Jessica Pan, Jeremy Goldwasser, Neha Verma, Wai Pan Wong, Muhammed Yavuz Nuzumlal, Benjamin Rosand, Yixin Li, Matthew Zhang, David Chang, R. Andrew Tay- lor, Harlan M. Krumholz, and Dragomir Radev. Neural Natural Language Processing for unstructured data in electronic health records: A review. Computer Science Review, 46:100511, 2022

[33] Leland McInnes, John Healy, Nathaniel Saul, and Lukas GroSSberger. UMAP: Uniform Manifold Approximation and Projection. Journal of Open Source Software, 3(29):861, 2018.

[34] Rico Sennrich, Barry Haddow, and Alexandra Birch. Neural machine translation of rare words with subword units. In Katrin Erk and Noah A. Smith, editors, Proceedings of the 54th Annual Meeting of the Association for Computational Linguistics (Volume 1: Long Papers), pages 17151725, Berlin, Germany, August 2016. Association for Computational Linguistics.

[35] Ashish Vaswani, Noam Shazeer, Niki Parmar, Jakob Uszkoreit, Llion Jones, Aidan N Gomez, L ukasz Kaiser, and Illia Polosukhin. Attention is All you Need. In I. Guyon, U. Von Luxburg, S. Bengio, H. Wallach, R. Fergus, S.

Vishwanathan, and R. Garnett, ed- itors, Advances in Neural Information Processing Systems, volume 30. Curran Associates, Inc., 2017.

[36] Leonardo Potenza, Giulia Guerrini, Giulia Di Lorenzo et al. A Trajectory-Adaptive Model of Early Palliative Care in AML and High-Risk MDS: Real-World Evidence on Core Components and Care Outcomes, Journal of Pain and Symptom Management, 2026, ISSN 0885-3924, https://doi.org/10.1016/j.jpainsymman.2026.05.019. (https://www.sciencedirect.com/science/article/pii/S0885392426008158)

[37] Earle CC, Park ER, Lai B, et al. Identifying potential indicators of the quality of end-of-life cancer care from administrative data. J Clin Oncol. 2003;21:11331138.

[38] Odejide OO, Cronin AM, Condron NB, et al. Barriers to quality end-of-life care for patients with blood cancers. J Clin Oncol. 2016;34:31263132.

[39] Potenza L, Efficace F, Borelli E, et al. Understanding challenges and barriers to quality end-of-life care for patients with hematologic malignancies: a GIMEMA survey. Ann Hematol. 2025;104:54235432.

[40] El-Jawahri A, LeBlanc T, VanDusen H, Traeger L, Greer JA, Pirl WF, Jackson VA, Telles J, Rhodes A, Spitzer TR, McAfee S, Chen YA, Lee SS, Temel JS. Effect of Inpatient Palliative Care on Quality of Life 2 Weeks After Hematopoietic Stem Cell Transplantation: A Randomized Clinical Trial. JAMA. 2016 Nov 22;316(20):2094-2103. doi: 10.1001/jama.2016.16786. PMID: 27893130; PMCID: PMC5421101.

[41] Justin J. Sanders et al. Palliative Care for Patients With Cancer: ASCO Guideline Update. J Clin Oncol 42, 2336-2357(2024). DOI:10.1200/JCO.24.00542