

# Prevalence of therapeutic and diagnostic procedures in the last 14 days of life in hospital patients: a single-center observational study from Germany

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**Background:** The opportunities available for maintaining and prolonging life in modern medicine give rise to medical-ethical dilemmas in patients at the end of life, raising the question of whether intensified treatment and diagnosis is appropriate in these patients. This affects hospital patients in particular.

**Methods:** This single-center cross-sectional study from Germany analyzed hospital records of all deceased patients of a university hospital who died between October 2016 and September 2017. The prevalence of therapeutic and diagnostic procedures during the last 14 days before death was determined. In-hospital transfer practices shortly before patients' deaths were also examined.

**Results:** A total of 468 hospital patients died. The mean age at death was 76.3±13.7 years; 47.0% [220] were female; 12.0% [56] died on the day of hospital admission, 41.9% [196] 1 to 6 days and 46.1% [216] more than 6 days later; the case mix index (CMI) was 4.6. The majority of patients {57.1% [267]} died on intensive care unit (ICU). Therapeutic and diagnostic procedures within the last 14 days before death: 30.3% [142] resuscitation, 28.6% [134] surgery, 10.9% [51] extracorporeal membrane oxygenation (ECMO), 23.7% [111] renal replacement therapy, 4.3% [20] tracheostomy, 2.8% [13] PTCA/cardiac stenting, 1.9% [9] chemotherapy, 29.3% [137] transfusion of packed red blood cells, 13.7% [64] transfusion of prothrombin complex concentrate, 5.3% [25] cardiac catheter examination, 7.5% [35] upper gastrointestinal endoscopy, 79.1% [370] chest X-ray, 41.9% [196] computed tomography. In-hospital transfer from ICU to PCU before patients' death: 1.5% (4/274 ICU patients).

**Conclusions:** Intensified therapeutic and diagnostic procedures are often performed at the end of life in hospital patients. Closer interdisciplinary cooperation between intensive care and palliative care would be beneficial to improve in-patient care for these patients.

Keywords: End-of-life care; hospital; prevalence; treatment; diagnostic; palliative care

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## Introduction

Due to demographic change with increasing life expectancy in most industrialized and many developing countries, hospitals are confronted with a growing number of old, multimorbid and chronically ill patients (1). At the same time, public demand for technologically advanced medical care is also increasing (2).

Medical progress is now improving the chance of survival of seriously ill patients even in clinical situations in which the process of dying used to be inexorable and death was inevitable. However, the opportunities of modern medicine are not free of medical-ethical conflicts (3,4). Particularly in patients with a very poor prognosis who are at the end of their lives, the question arises of whether medical treatment is appropriate (5-7). When is intensified therapy with the intention of curation still justified and when should the focus turn towards palliation?

In Germany, almost 19.4 million patients received inpatient treatment in hospitals in 2017 (8). More than 1,900 hospitals existed nationwide, including 35 university hospitals. A total of 497,182 hospital beds were provided, including 28,031 ICU beds. Hospital costs amounted to €105.7 billion, representing 28.1% of Germany's annual health-care expenditure of €376 billion (9).

A total of 427,917 patients died in hospitals in Germany in 2017, corresponding to 45.9% of all registered deaths (10). This means that hospitals were by far the most frequent place of death in Germany (11). Between 2007 and 2015, the proportion of patients receiving intensive-care treatment among all hospital deaths increased from 20.6% to 25.6% (12). Statistical model calculations are predicting a further increase in the absolute numbers of deaths in the German population in the coming decades (13).

The frequency with which intensified treatment and diagnosis are carried out in hospital patients shortly before death is receiving increasing scientific attention (14,15). Earle and colleagues have defined clinical quality indicators for cancer patients relative to overtreatment, mistreatment, and undertreatment at the end of life (16-19). Threshold values for treatment centers were established in the process—stating, for example, that less than 10% of cancer patients should have received chemotherapy within the last 14 days of life.

Following the publication of the oft cited Temel study (20), clinical quality indicators have gained importance internationally. Jennifer S. Temel and colleagues showed that including early palliative care in the treatment

of patients with metastatic non-small cell lung carcinoma (NSCLC) not only improves their quality of life and reduces anxiety and depression, but in addition leads to longer survival. A Cochrane meta-analysis confirmed that early palliative care could improve quality of life and reduce symptom intensity with no effects reaching statistical significance on survival (21). Some studies found that early palliative care also had a favorable impact on end-of-life care aggressiveness (22,23).

To date, there have been hardly any studies in Germany investigating the frequency of therapeutic and/or diagnostic procedures in hospital patients shortly before death (24-26). The aim of the present study was to analyze the prevalence of selected therapeutic and diagnostic procedures during the last 14 days of life among deceased hospital patients in a German university hospital. The place of death and in-hospital transfer practices shortly before the patients' deaths were also to be examined. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-2435).

#### **Methods**

#### Ethical approval

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the Ruhr University of Bochum (Germany) (No.: 17-6153). This approval also included a permission to analyse data from deceased patients for study purposes. Individual consent for this retrospective analysis was waived.

# Study design

The study is based on a retrospective single-center cross-sectional study design. All patients who died in hospital between October 1, 2016 and September 30, 2017 in a German university hospital were included in the study.

#### Study center

The university hospital is located in the Ruhr area in the federal state of North Rhine-Westphalia (Germany). It is a maximum-care hospital with a focus on surgery, consisting of 23 departments and specialist clinics. The hospital's core competency is based on the acute care and rehabilitation of severely injured and occupationally ill people. This includes

the care of polytrauma patients, the surgical treatment of complex injuries with a complicating healing process, and the treatment of spinal cord and severe burn injuries. There is also a large cardiac surgery department and a supraregional extracorporeal membrane oxygenation (ECMO) centre at the hospital. A palliative care unit and a palliative care consultant service were also present at the time when the study was carried out.

#### Data source

Patient data from the hospital information system (medico<sup>®</sup>; Cerner Deutschland GmbH, Idstein, Germany) were used as the data source, and were evaluated in anonymized form. Codes from the *Operationen- und Prozedurenschlüssel* (OPS, Operation and Procedure Classification System in Germany), diagnosis-related group (DRG) codes, patient Kardexes, nursing reports, patient files, discharge letters, and death certificates were used to obtain the best possible insight into the patient's disease status. Information on imaging diagnoses [chest X-rays, computed tomography, magnetic resonance imaging (MRI)] was obtained from the radiology information system (IMPAX 6.6.1.5003; Agfa Health Care GmbH, Bonn, Germany).

## Therapeutic and diagnostic procedures

In order to determine the prevalence of intensified therapeutic and diagnostic procedures in patients at the end of life, selected codes from the OPS, classified in accordance with the 2017 version of the International Classification of Procedures in Medicine (ICPM), were extracted from the hospital information system for the period of the last 14 days before the patient's death and analyzed. *Table 1* lists the selected medical procedures with corresponding OPS numbers (*Table 1*).

The date of performance from each procedure was recorded in order to identify medical procedures that had been performed during the 14 days prior to the patient's death. Plausibility checks showed almost 100% agreement between the documented date of the procedure and its actual performance in clinical reality.

## Patient sub-groups

The physician's indication determines whether or not a medical procedure is performed. To be able to interpret the results of the study adequately, we were faced with the methodological challenge of understanding why one medical procedure or another had been initiated by the physician in patients who were at the end of their lives. To approach this problem, we evaluated the study data from different clinical points of views—and guided by the idea that the medical indication is also influenced by the severity and life-threatening nature of the disease. In this context, we did not look exclusively at the data for all deceased but also performed sub-analyses for three specific patient groups outlined below:

(I) Patients with short survival time: we were interested in patients who died very shortly (≤48 h) after hospital admission. Our assumption was that these patients were in an acute life-threatening situation and therefore more likely to have received intensified medical treatment at the end of their life compared to patients with a survival time >48 hours.

(II) Patients with life-threatening emergencies: by definition, a life-threatening emergency was present if one of the following medical events had taken place:

- Presence of polytrauma and/or severe burn injury;
- Urgent surgical emergency;
- Use of Extra Corporeal Membrane Oxygenation (ECMO);
- Left cardiac catheterization as an emergency intervention;
- Upper gastrointestinal endoscopy as an emergency intervention;
- Out-of-hospital resuscitation shortly before hospital admission.

(III) Patients in palliative situations: the majority of palliative patients are represented by tumour patients with an advanced stage. Therefore, we focused on tumour patients who had been diagnosed with metastasis. The assumption was that advanced-stage tumour patients had received less frequently intensified interventions at the end of life than patients without a palliative situation.

## Place of death and in-hospital transfer practices

The hospital data were analyzed in relation to places of death of the deceased patients, which were classified as follows: 1, intensive care unit (ICU); 2, intermediate care unit (IMCU); 3, general ward (GW); 4, palliative care unit (PCU); 5, other (emergency room or operating room).

We also investigated in-hospital transfer practices for patients who were at the end of their lives. For this purpose, we identified those patients who had been transferred from

Table 1 Operation and Procedure Classification (OPS) codes for selected therapeutic and diagnostic procedures

Therapeutic procedures	OPS code	Diagnostic procedures	OPS code
Resuscitation	8-771	Chest X-ray	IMPAX (Agfa)
Surgery	5-01 to 5-92	СТ	3-20 to 3-26; IMPAX (Agfa)
Extracorporeal membrane oxygena (ECMO)	8-852.0, 8-852.3	MRI	3-80 to 3-84
Renal replacement therapy (RRT)	8-853 to 8-857, 8-85a	Transarterial left cardiac catheterization	1-275
Percutaneous transluminal coronary angioplasty (PTCA)/ coronary stenting (CS)	8.837	Tracheobronchoscopy Upper gastrointestinal endoscopy	1-62 1-63
Tracheostomy	5-311, 5-312		
Therapeutic puncture of the pleural cavity	8-152.1		
Therapeutic puncture of the abdominal cavity	8-153		
Gastrostomy (PEG placement)	8-431.2		
Chemotherapy	8-541, 8-542, 8-543, 8-544, 8-546, 8-547, 8-549, or 6-00 in combination with 8-54		
Transfusion – red blood cell concentrate (RBC)	8-800.c		
Transfusion – platelet concentrate (PC)	8-800.6, 8-800.d, 8-800.f, 8-800.g, 8.800.h		
Transfusion - normal plasma (P)	8.812.6		
Transfusion – synthetic plasma derivate (SPD)	8-810		
Transfusion – prothrombin-complex concentrate (PCC)	8-812.5		

CS, coronary stenting; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; MRI, magnetic resonance imaging; P, plasma (normal); PEG, percutaneous endoscopic gastrostomy; PC, platelet concentrate; PCC, prothrombin-complex concentrate; PTCA, percutaneous transluminal coronary angioplasty; RBC, red blood cell concentrate; RRT, renal replacement therapy; SPD, synthetic plasma derivate.

one ward to another within the last 14 days of life and used the last transfer date, including the transfer location.

## Statistical analyses

The frequencies of therapeutic and diagnostic procedures within the last 14 days before the patient's death are presented both in absolute numbers (procedures performed) and as percentages (patients treated). The prevalence of medical procedures was determined by calculating the number of patients with procedures (numerator) divided by the total number of deceased patients (denominator). The maximum number of procedures performed per patient was also recorded. This was easily determined for most procedures, but not for renal replacement therapy or

transfusions. RRT was evaluated by definition as a single measure if the treatment had been performed continuously without an interruption lasting more than 24 hours. In the case of transfusions, since the day of administration was well documented, but not the absolute quantity transfused (e.g., the amount of RBC transfused), the transfusion day was regarded as a single treatment unit.

The prevalence of medical procedures was determined for all deceased patients. In addition, the frequency of procedures performed was analysed for sub-groups (patients with survival time ≤48 or >48 h after hospital admission, patients with and without life-threatening emergencies, patients with and without a palliative situation).

Differences in frequency were tested using the chi-square test, or Fisher's exact test if there was a low frequency of less than 5 for the cell count. To take account of the global increase in the probability of alpha error (type 1 error) due to multiple testing in the same sample, the critical significance level (P=0.05) was divided by the number of statistical tests performed (Bonferroni correction).

We were interested in the time at which a medical intervention was last initiated in a patient before death. For this purpose, the observation period was divided into five-time contingents (day of death and 1, 2, 3–6, and 7–14 days before death). The date on which the procedure was last performed was determined and this event was assigned to the corresponding category.

The place where the procedure was performed was also analyzed. The data from the hospital information system on the place of treatment for each individual therapeutic procedure were evaluated for this purpose (ICU, IMCU, GW, PCU, emergency room, operating room, other location). The term "other location" here covered the following localities: cardiac catheter laboratory, endoscopy room, dialysis clinic (connected to the hospital). For diagnostic procedures, it was not always possible to allocate the location with certainty. All computed tomography (CT) and magnetic resonance imaging (MRI) examinations were carried out in specially designated radiology rooms. Similarly, transarterial left cardiac catheter examinations were performed exclusively in the cardiac catheter laboratory. The remaining procedures were carried out mainly on the requesting wards, but in some cases also in the relevant diagnostic units.

To determine if and when a patient was last transferred within the hospital during the last 14 days before death, the date of transfer and the discharging and admitting wards were noted. The data were assigned to time categories (day of death and 1, 2, 3–6, and 7–14 days before death) and then reported descriptively.

The statistical analyses were performed using the statistics software program IBM SPSS Statistics for Windows, version 26.

#### **Results**

# Deceased patients

A total of 468 patients died in the hospital during the 12-month period. Their mean age at death was 76.3 years. Approximately half of them were aged 80 or over. Deaths were slightly more frequent among men than women (53.0% vs. 47.0%). Twelve of 100 patients died on the day of

admission and only 26.7% survived more than 14 days. The mean hospitalization period was 12.3 days. The case mix index (CMI) was high at 4.6, with surgical patients showing an extremely high CMI of 8.3. Thirty point three percent of all deceased were by definition in an emergency situation. Sixty-nine point four percent of the deceased had been treated on ICU during hospital stay. In descending order, the five most frequent diagnoses were: chronic ischemic heart disease, sepsis, pneumonia, cancer, and dementia (*Table 2*).

# Place of death

More than half of the patients (57.1%) died at ICU, 7.1% at intermediate care unit, 20.5% at general ward, 13.7% at palliative care unit, 1.1% in the operating theatre, and 0.6% at the emergency room (*Figure 1*). Slightly more than half of the deceased (51.5%) received invasive ventilation treatment on the day of death; 9.8% died during ongoing ECMO treatment.

# Therapeutic and diagnostic procedures at the end of life

Patients received intensified medical measures and diagnostics within the last 14 days before death. In this context, the prevalence of inpatient resuscitation was 30.3%, and the proportion of patients who underwent surgery was 28.6%. Renal replacement procedures were initiated in 23.7%, and an indication for ECMO was given in 10.9% of the cases. In addition, transfusions were frequently initiated. For example, 29.3% of the patients received red blood cell concentrates (RBCs), 15.0% platelet concentrates (PCs), and 13.7% prothrombin-complex concentrates (PCCs). Chemotherapy was carried out in 1.9% of the patients at the end of their lives.

Chest X-rays were by far the most frequently requested diagnostic procedure. A total of 79.1% of the patients had X-rays, with the majority undergoing X-ray imaging several times. A mean of 4.3 X-rays were taken per patient. The maximum was 26 examinations per patient. Computed tomography (CT) was performed in 196 of the 468 patients (41.9%). Cardiac catheter examinations were performed in 5.3% of the patients, usually on an emergency basis. Endoscopy was carried out in 7.5%, with five of the 35 endoscopies involving emergencies (*Table 3*).

Patients with a survival time ≤48 h were almost twice as likely to undergo resuscitation in comparison with patients

Table 2 Characteristics of deceased hospital patients (n=468)

Characteristic	n	%	95% CI
Gender			
Women	220	47.0	42.5–51.5
Men	248	53.0	48.5–57.5
Age at death (y, mean/SD/median)	76.3/13.7/79.1		
Women	79.5/12.3/82.1		
Men	73.4/14.2/77.0		
<20 y	2	0.4	0.0–1.0
20–39 y	8	1.7	0.5–2.9
40–59 y	46	9.8	7.1–12.5
60–69 y	71	15.2	11.9–18.5
70–79 y	122	26.1	22.1–30.1
80–89 y	160	34.2	29.9–38.5
≥90 y	59	12.6	9.6–15.6
Hospital admission			
Elective	56	12.0	9.1–14.9
Transfer	87	18.6	15.1–22.1
Emergency/self-admission	325	69.4	65.2–73.6
IMCU or ICU treatment			
IMCU	132	28.2	24.1–32.3
ICU	325	69.4	65.2–73.6
Length of hospital stay (days)			
Total (mean/SD)	12.3/17.8		
ICU	7.3/11.8		
Department at discharge			
Surgery	173	37.0	32.6-41.4
Internal medicine	214	45.7	41.2–50.2
Neurology	18	3.8	2.1–5.5
Palliative care	63	13.5	10.4–16.6
Time from admission to death			
Death on day of admission	56	12.0	9.1–14.9
Death 1 day after admission	54	11.5	8.6–14.4
Death 2 days after admission	30	6.4	4.2-8.6
Death 3–6 days after admission	112	23.9	20.0–27.8
Death 7–14 days after admission	91	19.4	15.8–23.0
Death >14 days after admission	125	26.7	22.7–30.7

Table 2 (continued)

Table 2 (continued)

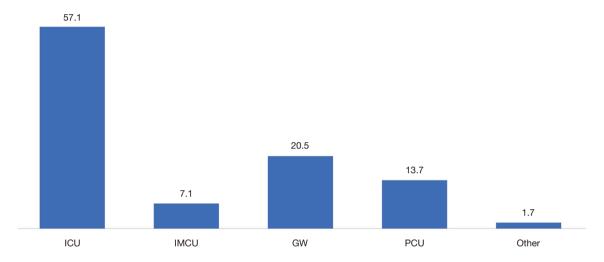
Characteristic	n	%	95% CI
Emergency intervention			
Emergency patients	142	30.3	26.1–34.5
Polytrauma/burns	21	4.5	2.6-6.4
Surgery	45	9.6	6.9–12.3
ECMO	51	10.9	8.1–13.7
Left cardiac catheterization	23	4.9	2.9–6.9
Upper gastrointestinal endoscopy	5	1.1	0.2-2.0
Out-of hospital CPR shortly before hospital admission	39	8.3	5.8–10.8
Case mix index (CMI)			
Total	4.6		
Patients discharged from surgery	8.3		
Patients discharged from internal medicine	2.6		
Patients discharged from neurology	2.2		
Patients discharged from palliative care	1.8		
Diagnosis			
Chronic ischemic heart disease	149	31.8	27.6–36.0
Acute myocardial infarction	56	12.0	9.1–14.9
Acute pulmonary embolism	6	1.3	0.3-2.3
Cardiac vitium	34	7.3	4.9–9.7
Endocarditis	13	2.8	1.3–4.3
Aortic dissection	12	2.6	1.2-4.0
Sepsis	114	24.4	20.5–28.3
Acute respiratory distress syndrome (ARDS)	28	6.0	3.8-8.2
Acute pneumonia	86	18.4	14.9–21.9
Chronic obstructive pulmonary disease	34	7.3	4.9–9.7
Cancer	76	16.2	12.9–19.5
Advanced cancer (metastases)	50	10.7	7.9–13.5
Renal failure stage 5 (GFR <15%)	18	3.8	2.1–5.5
Hepatic cirrhosis	8	1.7	0.5–2.9
Mesenteric ischemia	4	0.9	0.0–1.8
Ischemic stroke	31	6.6	4.4–8.8
Intracerebral hemorrhage	20	4.3	2.5-6.1
Dementia	59	12.6	9.6–15.6
Accident/trauma/fall	52	11.1	8.3–13.9
Polytrauma	13	2.8	1.3–4.3

Table 2 (continued)

Table 2 (continued)

Characteristic	n	%	95% CI
Burns	8	1.7	0.5–2.9
Attempted suicide	4	0.9	0.0–1.8
Terminal situation			
Invasive ventilation on day of death	241	51.5	47.0–56.0
Died during ongoing ECMO	46	9.8	7.1–12.5

ARDS, acute respiratory distress syndrome; CMI, case mix index; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; ICU, intensive-care unit; IMCU, intermediate-care unit; SD, standard deviation.



**Figure 1** Places of death of deceased hospital patients. GW, general ward; ICU, intensive care unit; IMCU, intermediate care unit; PCU palliative care unit.

with a survival time >48 h (43.6% vs. 24.7%; P=0.001). Surgery, endoscopy, bronchoscopy, chest X-ray, and CT examinations were also more frequent.

Emergency patients showed similar findings. Resuscitation was carried out in 47.2%. Half of them (50.7%) had to undergo surgery, and more than one-third (35.9%) received ECMO. In addition, these patients had transfusions more often than patients without emergency conditions. The proportion of patients who received left heart catheter examinations was also significantly higher among emergency patients (16.2% vs. 0.6%; P=0.001).

Palliative cancer patients with advanced stage received significantly fewer intensified therapeutic and diagnostic procedures. The resuscitation rate among these patients was 2.0%. Surgery was performed three times, and renal replacement therapy six times less frequently (*Table 4*).

Figure 2 provide an overview of the last procedures

initiated before the patients' deaths. The procedures were performed on the day of death in 70.4% of the patients who received resuscitation and 17.2% of those who underwent surgery. In 31.4% of the ECMO patients, the indication for starting the procedure was established on the day of death. The frequency of transfusions performed on the day of death corresponded approximately to the frequency of operations on the day of death. Chest X-rays were performed in one in three and CT scans in one in seven of the patients in whom these diagnostic procedures were carried out on the day of death (*Figure 2*).

*Table 5* clearly show that a large proportion of the therapeutic and diagnostic measures at the end of life were primarily performed in ICU patients (*Table 5*).

A total of 364 patients were transferred within the hospital during the last 14 days of life, with 119 patients being transferred from the emergency room to a hospital

Table 3 Therapeutic and diagnostic procedures at the end of life

Dunashiwas		N=46	8	Abs.	Max.
Procedures —	n	%	95% CI	n	n
Therapeutic procedures					
Resuscitation	142	30.3	26.1–34.5	161	2
Surgery	134	28.6	24.5–32.7	193	5
Extracorporeal membrane oxygenation (ECMO)	51	10.9	8.1–13.7	51	1
Renal replacement therapy (RRT)	111	23.7	19.8–27.6	115	4
Percutaneous transluminal coronary angiography (PTCA/CS)	13	2.8	1.3–4.3	13	1
Tracheostomy	20	4.3	2.5–6.1	20	1
Pleura puncture	12	2.6	1.2-4.0	12	1
Ascites puncture	5	1.1	0.2–2.0	5	1
Percutaneous endoscopic gastrostomy (PEG)	0	0.0	0.0-0.0	0	0
Chemotherapy	9	1.9	0.7–3.1	9	1
Transfusion - red blood cell concentrate (RBC)	137	29.3	25.2–33.4	196	4
Transfusion - platelet concentrate (PC)	70	15.0	11.8–18.2	86	2
Transfusion - normal plasma (P)	20	4.3	2.5–6.1	20	1
Transfusion - prothrombin-complex concentrate (PCC)	64	13.7	10.6–16.8	74	3
Transfusion - synthetic plasma derivate (SPD)	95	20.3	16.7–23.9	119	3
Diagnostic procedures					
Chest X-ray	370	79.1	75.4–82.8	1,599	26
Computed tomography (CT)	196	41.9	37.4–46.4	284	6
Magnetic resonance imaging (MRI)	6	1.3	0.3–2.3	6	1
Left heart catheterization (LHC)	25	5.3	3.3–7.3	25	1
Tracheo-bronchoscopy	55	11.8	8.9–14.7	70	3
Upper gastrointestinal endoscopy	35	7.5	5.1–9.9	38	2

CS, coronary stenting; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; LHC, left heart catheterization; MRI, magnetic resonance imaging; OR, odds ratio; P, normal plasma; PEG, percutaneous endoscopic gastrostomy; PC, platelet concentrate; PCC, prothrombin-complex concentrate; PTCA, percutaneous transluminal coronary angiography; RBC, red blood cell concentrate; RRT, renal replacement therapy; SPD, synthetic plasma derivate.

ward on the day of admission (61.4% to the ICU, 5.0% to the IMCU, 31.9% to a general ward, 1.7% to a palliative care unit). In all, 245 patients were transferred from one ward to another, representing 52.4% of all the deceased patients. Forty-five of them were transferred on the day of death—mostly from a general ward to ICU. Although more than half of the 468 patients died in the ICU in hospital, only four were transferred from the ICU to PCU before their death (*Table 6*).

#### **Discussion**

The study shows that there was a high prevalence of intensified therapeutic and diagnostic procedures during the last 14 days of life among patients in a German university hospital. Of those procedures, it was found that 30.3% of the deceased had been resuscitated within the last two weeks of life, 28.6% had undergone surgery, 23.7% had received renal replacement therapy, 29.3% had been transfused with

Table 4 Medical procedures at the end of life relative to survival time, emergency patients, and advanced cancer (metastases)

	Surviv	al time		Emergen	cy patient		Advance	ed cancer	
Procedures	≤48 h, N=140, % [n]	>48 h, N=328, % [n]	Р	Yes, N=142, % [n]	No, N=326, % [n]	Р	Yes, N=50, % [n]	No, N=418, % [n]	Р
Therapeutic procedur	res			-				-	
Resuscitation	43.6 [61]	24.7 [81]	0.001*	47.2 [67]	23.0 [75]	0.001*	2.0 [1]	33.7 [141]	0.001*
Surgery	19.3 [27]	32.6 [107]	0.004	50.7 [72]	19.0 [62]	0.001*	10.0 [5]	30.9 [129]	0.001*
ECMO	14.3 [20]	9.5 [31]	0.145	35.9 [51]	0.0 [0]	-	0.0 [0]	12.2 [51]	-
RRT	18.6 [26]	25.9 [85]	0.097	40.8 [58]	16.3 [53]	0.001*	4.0 [2]	26.1 [109]	0.001*
PTCA/CS	2.1 [3]	3.0 [10]	0.763	8.5 [12]	0.3 [1]	0.001*	0.0 [0]	3.1 [13]	_
Tracheostomy	0.7 [1]	5.8 [19]	0.011	7.0 [10]	3.1 [10]	0.078	0.0 [0]	4.8 [20]	_
Pleural puncture	0.0 [0]	3.7 [12]	_	1.4 [2]	3.1 [10]	0.362	0.0 [0]	2.9 [12]	-
Ascites puncture	0.0 [0]	1.5 [5]	_	2.1 [3]	0.6 [2]	0.166	0.0 [0]	1.2 [5]	-
Gastrostomy [PEG]	0.0 [0]	0.0 [0]	-	0.0 [0]	0.0 [0]	_	0.0 [0]	0.0 [0]	_
Chemotherapy	1.4 [2]	2.1 [7]	0.999	0.0 [0]	2.8 [9]		18.0 [9]	0.0 [0]	-
Transfusion - RBC	28.6 [40]	29.7 [97]	0.912	52.5 [74]	19.3 [63]	0.001*	14.0 [7]	31.2 [130]	0.013
Transfusion - PC	14.3 [20]	15.2 [50]	0.888	35.9 [51]	5.8 [19]	0.001*	0.0 [0]	16.7 [70]	-
Transfusion - P	0.7 [1]	5.8 [19]	0.011	10.6 [15]	1.5 [5]	0.001*	0.0 [0]	4.8 [20]	-
Transfusion - PCC	12.9 [18]	14.0 [46]	0.771	31.7 [45]	5.8 [19]	0.001*	0.0 [0]	15.3 [64]	-
Transfusion - SPD	15.7 [22]	22.3 [73]	0.132	42.3 [60]	10.7 [35]	0.001*	2.0 [1]	22.5 [94]	0.001*
Diagnostic procedure	s								
Chest X-ray	62.1 [87]	86.3 [283]	0.001*	81.0 [115]	78.2 [255]	0.538	44.0 [22]	83.3 [348]	0.001*
CT	31.4 [44]	46.3 [152]	0.003	48.6 [69]	39.0 [127]	0.054	20.0 [10]	44.5 [186]	0.001*
MRI	0.7 [1]	1.5 [5]	0.674	1.4 [2]	1.2 [4]	0.999	2.0 [1]	1.2 [5]	0.494
LHC	5.7 [8]	5.2 [17]	0.824	16.2 [23]	0.6 [2]	0.001*	0.0 [0]	6.0 [25]	-
Bronchoscopy	3.6 [5]	15.2 [50]	0.001*	14.1 [20]	10.7 [35]	0.349	2.0 [1]	12.9 [54]	0.019
Endoscopy	2.1 [3]	9.8 [32]	0.003	12.0 [17]	5.5 [18]	0.210	0.0 [0]	8.4 [35]	_

<sup>\*</sup> significant result (according to Bonferroni correction). CI, confidence intervals; CS, coronary stenting; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; GOF, goodness of fit; LHC, left heart catheterization; MRI, magnetic resonance imaging; OR, odds ratio; PEG, percutaneous endoscopic gastrostomy; PPSB, prothrombin–proconvertin–Stuart factor–antihemophilic factor B; PTCA, percutaneous transluminal coronary angiography.

red blood cells and 20.3% transfused with synthetic plasma derivatives. In 10.9% of the cases the decision for ECMO had been made. In terms of diagnostic procedures, 41.9% of the patients had received at least one CT scan and 79.1% had received at least one conventional X-ray examination. Seventy point four percent of patients who were resuscitated and 31.4% of patients with ECMO therapy

died on the same day the intervention was initiated. Most of the procedures were performed in the ICU, where more than half of all patients died. Only four patients had been transferred from the intensive care unit to the palliative care unit prior to death.

The study involved patients in a university hospital with a focus on surgery expertise. The hospital's core competencies

	Res	Resuscitation (N=142)	N=142)		Surgery (N=134)	134)		ECMO (N=51)	51)		RRT (N=111)	1		PTCA/CS (N=13)	=13)
	С	%	% cum.	L	%	% cum.	С	%	% cum.	드	%	% cum.	L	%	% cum.
Day of death	100	70.4	70.4	23	17.2	17.2	16	31.4	31.4	27	24.3	24.3	2	15.4	15.4
1 day before death	24	16.9	87.3	29	21.6	38.8	7	21.6	52.9	33	29.7	54.1	-	7.7	23.1
2 days before death	2	3.5	8.06	13	9.7	48.5	4	7.8	8.09	14	12.6	2.99	0	0.0	23.1
3–6 days before death	8	5.6	92.6	33	24.6	73.1	7	21.6	82.4	22	19.8	86.5	7	53.8	6.92
7-14 days before death	2	3.5	100	36	26.9	100	6	17.6	100	15	13.5	100	က	23.1	100
	Tra	Tracheostomy (N=20)	(N=20)	Pleura	ira puncture (N=12)	(N=12)	Asci	Ascites puncture (N=5)	(S=N) e	PEC	PEG placement (N=0)	t (N=0)	5	Chemotherapy (N=9)	(6=N)
	С	%	% cum.	۵	%	% cum.	٦	%	% cum.	۵	%	% cum.	L	%	% cum.
Day of death	-	5.0	5.0	-	8.3	8.3	0	0:0	0.0	0	0.0	0.0	0	0.0	0.0
1 day before death	2	10.0	15.0	0	0.0	8.3	-	20.0	20.0	0	0.0	0.0	0	0.0	0.0
2 days before death	2	10.0	25.0	0	0.0	8.3	-	20.0	40.0	0	0.0	0.0	0	0.0	0.0
3-6 days before death	9	30.0	55.0	4	33.3	41.7	-	20.0	0.09	0	0.0	0.0	က	33.3	33.3
7-14 days before death	6	45.0	100	7	58.3	100	2	40.0	100	0	0.0	0.0	9	66.7	100
	Transf	Transfusion - RBC (N=138)	C (N=138)	Trans	Transfusion - PC (N=70)	(N=70)	Trar	Transfusion - P (N=20)	(N=20)	Trans	Transfusion - PCC (N=64)	C (N=64)	Trans	Transfusion - SPD (N=95)	(96=N) C
	۲	%	% cum.	۵	%	% cum.	۵	%	% cum.	ᆮ	%	% cum.	۵	%	% cum.
Day of death	21	15.2	15.2	6	12.9	12.9	2	25.0	25.0	12	18.8	18.8	16	16.8	16.8
1 day before death	35	25.4	40.6	17	24.3	37.1	7	35.0	0.09	21	32.8	51.6	26	27.4	44.2
2 days before death	14	10.1	50.7	80	11.4	48.6	-	5.0	65.0	7	10.9	62.5	13	13.7	6.73
3-6 days before death	38	27.5	78.3	23	32.9	81.4	4	20.0	85.0	11	17.2	7.67	21	22.1	80.0
7-14 days before death	30	21.7	100	13	18.6	100	3	15.0	100	13	20.3	100	19	20.0	100
	Ь	Chest X-ray (N=370)	1=370)		CT (N=196)	3)		MRI (N=6)	(		LHC (N=25)	5)	Upper	Upper GI endoscopy (N=35)	py (N=35)
	u	%	% cnm.	L	%	% cum.	n	%	% cum.	L	%	% cum.	L	%	% cum.
Day of death	114	30.8	30.8	28	14.3	14.3	-	16.7	16.7	5	20.0	20.0	-	2.9	2.9
1 day before death	93	25.1	55.9	48	24.5	38.8	1	16.7	33.3	3	12.0	32.0	7	20.0	22.9
2 days before death	34	9.2	65.1	17	9.2	47.4	0	0.0	33.3	4	16.0	48.0	4	11.4	34.3
3-6 days before death	83	22.4	97.8	63	32.1	80.1	2	33.3	66.6	8	32.0	80.0	5	14.3	48.6
7-14 days before death	46	12.4	100	39	19.9	100	2	33.3	100	2	20.0	100	18	51.4	100
Cum. cumulative: CS. coronary stenting: CT. computed tomography:	narv stent	ina: CT, coi	monted tomo	oraphy; E	ECMO. extra	scorporeal m	embrane	oxvaenatior	ECMO. extracorporeal membrane oxvdenation: Gl. gastointestinal: LHC. left heart catheterization: MBl. magnetic resonance	testinal:	LHC. left he	art catheteri	zation: ME	3. magnetic	resonance

Oum., cumulative; CS, coronary stenting; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; GI, gastointestina; LHC, left heart catheterization; MRI, magnetic resonance imaging; P, plasma (normal); PEG, percutaneous endoscopic gastrostomy; PC, platelet concentrate; PCC, prothrombin-complex concentrate; PTCA, percutaneous transluminal coronary angioplasty; RBC, red blood cell concentrate; RRT, renal replacement therapy; SPD, synthetic plasma derivate.

Figure 2 Last therapeutic/diagnostic procedures initiated at the end of life relative to the patient's remaining survival time.

Table 5 Absolute numbers of therapeutic procedures carried out at the end of life relative to the location of the procedure

Procedures	Total Abs./ Max.	ICU Abs./ Max.	IMCU Abs./ Max.	GW Abs./ Max.	PCU Abs./ Max.	ER Abs./ Max.	OT Abs./ Max.	Other Abs./ Max.
Therapeutic procedures								
Resuscitation	161/2	88/2	10/1	27/1	0/0	17/1	15/1	4/1
Surgery	193/5	3/1	-	-	-	-	190/5	0/0
ECMO	51/1	47/1	0/0	0/0	0/0	1/1	3/1	0/0
RRT	115/4	108/1	0/0	0/0	0/0	0/0	0/0	4/4
PTCA/CS	13/1	0/0	0/0	0/0	0/0	0/0	0/0	13/1
Tracheostomy	20/1	20/0	0/0	0/0	0/0	0/0	0/0	0/0
Ascites puncture	5/1	2/1	2/1	0/0	1/1	0/0	0/0	0/0
Pleura puncture	12/1	5/1	3/1	4/1	0/0	0/0	0/0	0/0
Gastrostomy (PEG)	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Chemotherapy	9/1	0/0	0/0	7/1	0/0	0/0	-	2/1
Transfusion - RBC	196/4	78/2	10/1	7/1	3/1	2/1	94/3	2/1
Transfusion - PC	86/2	35/2	5/2	1/1	0/0	0/0	45/2	0/0
Transfusion - P	20/1	16/1	0/0	0/0	0/0	0/0	4/1	0/0
Transfusion - PCC	74/3	23/2	1/1	0/0	0/0	1/1	49/3	0/0
Transfusion - SPD	119/3	56/2	3/1	2/1	0/0	1/1	57/3	0/0
Diagnostic procedures								
Chest X-ray	1,599/26	1,191/26	131/10	131/4	4/2	142/3	_	_
СТ	284/6	146/5	26/3	47/3	1/1	64/1	_	_
MRI	6/1	2/1	1/1	3/1	0/0	0/0	_	_
LHC	25/1	20/1	0/0	1/1	0/0	5/1	_	-
Tracheobronchoscopy	70/3	58/3	7/1	5/1	0/0	0/0	_	-
Upper GI endoscopy	38/2	29/2	2/1	7/1	0/0	0/0	_	-

Data are given as absolute numbers/maximum procedures per person. CS, coronary stenting; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; ER, emergency room; GW, general ward; ICU, intensive-care unit; IMCU, intermediate care unit; GI, gastointestinal; LHC, left heart catheterization; MRI, magnetic resonance imaging; OT, operating theatre; PCU, palliative care unit; PEG, percutaneous endoscopic gastrostomy; P, normal plasma; PC, platelet concentrate; PCC, prothrombin-complex concentrate; PTCA, percutaneous transluminal coronary angiography; RBC, red blood cell concentrate; RRT, renal replacement therapy; SPD, sythetic plasma derivate.

included polytrauma care, surgery of complex accident injuries with complicative course, and the treatment of spinal cord and severe burn injuries. A large cardiac surgery department and a supra-regional ECMO centre were also present at the hospital.

The patients examined had an average case mix index of 4.6, reflecting the high severity of the patient cases and also the large amount of economic resources expended. The

expenditure was mainly on ICU patients. The length of the hospital stays also indicates the severity of the diseases. Approximately one in 10 died on the day of admission, almost one-third within the first 2 days after admission, and slightly more than half after one week.

Our data show that emergency patients underwent resuscitation, surgery, transfusion, and radiological diagnosis more frequently than non-emergency patients. Similarly,

Table 6 Last in-hospital transfer relative to the patient's remaining survival time

T	1		1	3									
	¢ GW GW	GW → PCU	GW →	GW →	TWCU → GW	IMC ↓	↑ NON ICO	CU →	ICU →	↑ IMCU	↑ <u>10</u> 1	Other	Total
	(N=16)	(N=30)	(N=15)	(N=65)	(N=19)	(N=3)	(N=46)	(N=20)	(N=4)	(N=12)	(N=13)	(N=Z)	(N=Z45)
Day of death, n (%)	1 (6.3)	3 (10.0)	1 (6.7)	21 (32.3)	2 (10.5)	0.0) 0	8 (17.4)	3 (15.0)	1 (25.0)	1 (8.3)	3 (23.1)	1 (50.0)	45 (18.4)
1 day before death, n (%)	3 (18.8)	8 (26.7)	3 (20.0)	8 (12.3)	2 (10.5)	1 (33.3)	12 (26.1)	8 (40.0)	3 (75.0)	1 (8.3)	3 (23.1)	1 (50.0)	53 (21.6)
2 days before death, n (%)	3 (18.8)	5 (16.7)	2 (13.3)	9 (13.8)	4 (21.1)	0.0) 0	4 (8.7)	3 (15.0)	0.0) 0	1 (8.3)	0.0) 0	0.0) 0	31 (12.7)
3–6 days before death, n (%)	5 (31.3)	7 (23.3)	4 (26.7)	11 (16.9)	9 (47.4)	2 (66.7)	9 (19.6)	3 (15.0)	0 (0.0)	5 (41.7)	1 (7.7)	0 (0.0)	56 (22.9)
7-14 days before death, n (%)	1 (6.3)	5 (16.7)	4 (26.7)	8 (12.3)	1 (5.3)	0.0) 0	5 (10.9)	2 (10.0)	0.0) 0	1 (8.3)	2 (15.4)	0 (0.0)	29 (11.8)
>14 days before death, n (%)	3 (18.8)	2 (6.7)	1 (6.7)	8 (12.3)	1 (5.3)	0 (0.0)	8 (17.4)	1 (5.0)	0.0) 0	3 (25.0)	4 (30.8)	0.0) 0	31 (12.6)

GW, general ward; ICU, intensive care unit; IMCU, intermediate care unit; Other, died in operating room; PCU, palliative care unit.

a high proportion of patients who died within 48 hours of admission to hospital underwent resuscitation and/or surgery. This is not surprising, as half of these patients were in an emergency situation. In contrast, advanced cancer patients in a palliative situation received significantly fewer diagnostic and therapeutic procedures. Nevertheless, 18.0% of the cancer patients still received chemotherapy during the last two weeks of life.

Our findings are consistent with similar studies on

Our findings are consistent with similar studies on inpatients, which predominantly focused on tumour patients (24-28). In contrast, our patient sample differed in that we carried out the investigation on patients of a university hospital with a focus on trauma surgery.

More than half of the patients died on the intensive care unit, one in five on a general ward and about one in eight at the palliative care unit. This illustrates very clearly that intensive care medicine does not only face the challenge of stabilising acute life-threatening conditions but also requires a high level of expertise in end-of-life care. Epidemiological data affirms this point of view. A retrospective cohort study from the USA, using a 20% random sample of deceased Medicare beneficiaries aged 66 years and older, demonstrated that the proportion of deaths in patients with ICU care in the last month of life had increased from 24.3% in 2000 to 29.2% in 2009 and had stabilised between 2009 and 2015 at 29.0% (29). In Germany, with a total population of about 83 million people in 2019, the hospital is the most common place of death, with about half of all deaths occurring in this institution (8,11). Similar to the US data, an increase in hospital deaths with ICU care could also be observed in Germany between 2007 (20.6%) and 2015 (25.6%). The increasing trend of deaths involving ICU care was most marked in patients aged 65 years and older. In this age group, the number of hospital deaths involving ICU care increased approximately three times faster than the number of overall hospital deaths (12).

Due to the modern possibilities of intensive care medicine, there is a real threat that medical action will primarily concentrate on what is medically and technically feasible, thereby exceeding the limits of what is medically and ethically justifiable, and that too little attention will be paid to the needs and concerns of patients and their relatives. Our study data confirm this potential risk of "technical apparatus medicine", as we were able to show that hospital patients at the end of life received a very high proportion of intensified diagnostic and therapeutic procedures. In order to recognise the limits of technical medicine, medical expertise on the course and prognosis of

a disease and the recognition of an incipient dying situation is of crucial importance. In fact, if the course of the disease has actually progressed to the point where an incurable situation leading to death is imminent, the patient's quality of life and well-being should be the only considerations for medical action. In this context, interventions that would merely delay the process of dying or would only represent an additional burden for the patient should be avoided (30). Failure to do so is referred to as excessive care or overcommitment to care at the end of life. Scientific studies show that medical overtreatment is a real fact (31-33). For example, members of the American Medical Association (AMA) who were surveyed estimated that up to one-fifth of overall medical care was unnecessary (34). Nurses and doctors working in intensive care units in Europe expressed similar views (35).

The following aspects may contribute to overtreatment: high expectations of treatment on the part of patients and/ or relatives (36-39); supply-induced demand for medical services (40); the patient's social circumstances (e.g., living alone) (41); medical training that is primarily oriented towards action and less towards omission; prognostic uncertainties regarding the further course of the disease; overestimation of medical options for action; physicians' fear of misjudging the treatment situation (34,42); failure of physicians to accept fatal disease courses (43); and a lack of prior medical findings. Financial incentives for doctors and hospitals—and incentive-compliant behavior on their part—can also lead to overtreatment (44).

Palliative care is patient and family-centered care with the aim of optimizing quality of life by anticipating, preventing, and treating suffering, and providing comprehensive management of patients facing incurable diseases. Moreover, palliative care focuses on issues including symptom distress (physical, psychological, spiritual), and capacity to communicate and share decisionmaking. Although the aims of palliative care and critical care may initially seem divergent, values and goals in critical care and palliative care are similar, as saving or prolonging life may conciliate with alleviating suffering and improving quality of life and death. Of course, the primary goal of each discipline is the secondary goal of the other. In everyday clinical practice, critical care physicians are frequently confronted with changes in therapy goals, in the context of which an initially curative treatment is converted into palliative treatment. A survey among intensivists revealed that 35% felt unsure about this decision (45). This is just one aspect of how interdisciplinary cooperation between

intensive medicine and palliative medicine could improve the care of critically ill and/or dying patients.

The benefit of early involvement of palliative care in the treatment of patients with incurable diseases is nowadays undisputed and well supported by evidence (20-23,46,47). For example, patients who receive early palliative care have fewer physical and psychological symptoms and an improved perception of their disease prognosis in comparison with patients who do not receive such care. It has also been shown that this reduces hospital admissions, reduces the length of hospital stays, minimizes aggressive treatment at the end of life, and saves costs in the health-care sector. In addition, the medical colleagues of palliative physicians can benefit from their assessment of the prognosis and timely recognition of the terminal phase, among other things.

In Germany, there are about 2,000 hospitals. Of these, about 17% have a palliative care unit and less than 4% offer an inpatient palliative care service (48). Accordingly, only a minority of German hospitals currently have the possibility to offer inpatient specialised palliative care. The mobile inpatient palliative care service plays an important role in the interdisciplinary collaboration with other medical departments of the hospital by providing specialised palliative counselling, support and co-treatment for patients and their families outside the palliative care unit. The university hospital to which the study analyses refers to also had a palliative care unit and a palliative care consultant service. Of the 468 deceased patients, 13.7% died at the palliative care unit. More detailed analyses showed that predominantly patients with internal diseases (tumour patients, multimorbid patients) followed by neurological diseases (patients with stroke or intracerebral haemorrhage) died on the palliative care unit. Although the hospital had a surgical focus, hardly any surgical patients in palliative situations were transferred to the palliative care unit. The analysis of intra-hospital transfer practices within the last fourteen days of life before death yielded even more drastic results. Although the ICU was the location in which most of the patients were treated at the end of their lives, and more than half of the patients died there, transfer of a patient from the ICU to the palliative care unit only occurred in four cases. This makes it clear that interdisciplinary collaboration between intensive medicine and palliative medicine needed to be improved in the study center. A descriptive study from Germany conducted at 16 Comprehensive Cancer Centres (CCC) showed that cooperation between intensive care and palliative care is not only a local but also an overarching problem (49). In 2016,

the median of intensive care patients with palliative care consultations was 33 (minimum 0, maximum 100), only nine patients (median) were transferred from an intensive care unit to a palliative care unit (minimum 1, maximum 30). Multidisciplinary ward rounds by both intensive and palliative care staff were available in only two CCCs on a regular basis. Two CCCs implemented screening tools to integrate specialized palliative care into intensive care.

Barriers to the sharing of patient care between intensive care and palliative care specialists are complex and are often difficult to determine in individual cases. However, there is often a misunderstanding of the term "palliative care," which is regarded as being exclusively synonymous with terminal care (50). Some physicians also believe that merely mentioning the term "palliative medicine" will deprive the patient of any hope and that the term is associated with the stigma of death. In that view, including a palliative care team in patient care would simply represent an additional burden for the patient (51).

What opportunities are available for integrating palliative care into ICU structures? Conceivable approaches might include, for example: a mandatory participation of a team member from the inpatient palliative care service (palliative care physician or palliative care nurse) in the daily ward round on ICU and the use of a specific screening tool to identify ICU patients and family members with palliative care needs (52,53). The consistent involvement of ICU nursing staff can also help to detect patients in need of palliative care without having to set rigid criteria. It would also be useful to establish a standardised procedure for requesting palliative care services on ICU. More detailed and specific information about palliative medicine and communicative skills should also be provided during basic training for physicians and nurses. A look at the literature shows that these proposals have already been implemented successfully in some hospitals (54-58).

#### Limitations

This single-center study was conducted at a German university hospital providing maximum care. Accordingly, the results are not transferable to hospitals that provide basic and standard care. The study design was based on a cross-sectional survey. Although this methodological approach is well suited for hypothesis generation, it is not possible to draw any causal conclusions from it. In some cases, important information was lacking that might have influenced the use of more intensive therapy and/or

diagnostic procedures at the end of life, such as the patient's general physical condition or treatment preference. In addition, information on therapy limitations was not always strictly documented by the physicians. In individual cases it was thus not always easy to deduce the reasons for a specific treatment and/or diagnostic procedure at the end of life from the data available in the hospital information system.

#### **Conclusions**

This single-center study shows, that patients who are treated in a maximum-care university hospital at the end of their lives undergo large numbers of intensified therapeutic and diagnostic procedures in the last two weeks of their lives. This particularily applies to intensive care patients. Although there is evidence that the integration of palliative medicine expertise improves the care of critically ill and dying hospital patients, our study results demontrate that there are still deficits in interdisciplinary cooperation between intensive care medicine and other medical disciplines and palliative medicine in the hospital.

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#### **Footnote**

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the Ruhr University of Bochum (Germany)

(No.: 17-6153). This approval also included a permission to analyse data from deceased patients for study purposes. Individual consent for this retrospective analysis was waived.

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