

## CORRESPONDENCE OPEN



# Prospective systematic classification of causes of death in the course of multiple myeloma

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## INTRODUCTION

Multiple Myeloma (MM) is a hematological malignancy characterized by the clonal expansion of bone-marrow plasma cells with an annual incidence rate of about 9/100,000 (2020) in Germany [1], accounting for ~1.4% of newly diagnosed cancer and ~1.8% of all cancer-related deaths. Globally, an age-standardized-incidence of 1,8/100,000 was documented for 2022 [2]. Despite diagnostic and therapeutic advancements, MM remains largely incurable with an average relative five-year-survival rate of ~57% in Germany [1].

As novel targeted therapies are introduced, therapy-associated complications such as acute toxicity, immunosuppression-related infections and second primary malignancies (SPM) have increased [3–6]. We established a classification system for causes of death (COD) in MM [7] which was since applied prospectively in a large patient cohort from two randomized phase 3 clinical trials, GMMG-HD6 (NCT02495922) [8] and GMMG-HD7 (NCT03617731) [9, 10], and the Heidelberg-MM-registry (Heidelberg University Hospital, Heidelberg, Germany) [7].

This study seeks to elucidate COD trajectories, identify patterns of COD fluctuations, and reveal notable COD trends to inform clinical decision-making at different times during MM therapy and follow-up, by leveraging prospective employment of COD categorization by its relation to MM and the system organ class (SOC) as defined by the MedDRA terminology.

## MATERIAL AND METHODS

### Patients and consent

A total of 617 MM patients who died during follow-up from 06/2011 until 01/2024 were prospectively assessed. Patients gave written informed consent to data collection and analysis in the Heidelberg-MM-registry (ethics-number: S-096/2017) and/or the GMMG-HD6 (NCT02495922) [8] or GMMG-HD7 (NCT03617731) [9, 10] trials. All methods were performed in accordance with the relevant ethics guidelines and regulations.

### COD classification and definitions

COD information was gathered from medical documentation, then assigned one of the following categories by on-site medical personnel and monitored centrally by reviewing the available documentation within 90 days before time of death (JJ, BY, UB, KJG, EMK, and EKM), as previously reported [7]: (I) MM-dependent, (II) MM-independent, (III) not attributable to (I)/(II), and (IV) unknown. Additionally, (I) was further subdivided into (IA) MM-progression-related, (IB) therapy-related, and (IC) not attributable to (IA)/(IB). COD were then classified into System Organ Class

(SOC) and primary terms (PT) as per MedDRA terminology [11]. Unknown COD (IV), making up 19% (n = 117/617) of cases, were excluded from further analyses.

Survival time was defined from date of MM-specific therapy start until date of death. The first day of the respective month was used when exact day was unknown.

### Statistical methods

Analyses were performed using the R statistical software (version 4.4.1; [www.r-project.org](http://www.r-project.org), Vienna, Austria). Visualization was performed with ggplot2, ggforce, cowplot and survminer. Loess-regression curves were fitted alongside 95%-confidence-interval. Kaplan-Meier survival plots and COX models for survival estimation and calculation of associated hazard-ratios were fitted using the survival and survminer packages. Competing risk analyses were performed using the cmprsk package.

For bar plots, SOC and COD (as PT) terms other than the top-5 were summarized as “Others”.

For the flow plot, percentual shares and total counts of the top-5 SOC and top-10 COD (as PT) were calculated for the entire dataset. Remaining terms were summarized as “Other”.

For COD and SOC term distributions by survival or year of death, data was subset by category, then the top-5 terms were selected for display. If terms were tied, all tied terms were displayed. Datapoints were shown by year, except before 2014 and after 2023 which were summarized as two separate categories respectively.

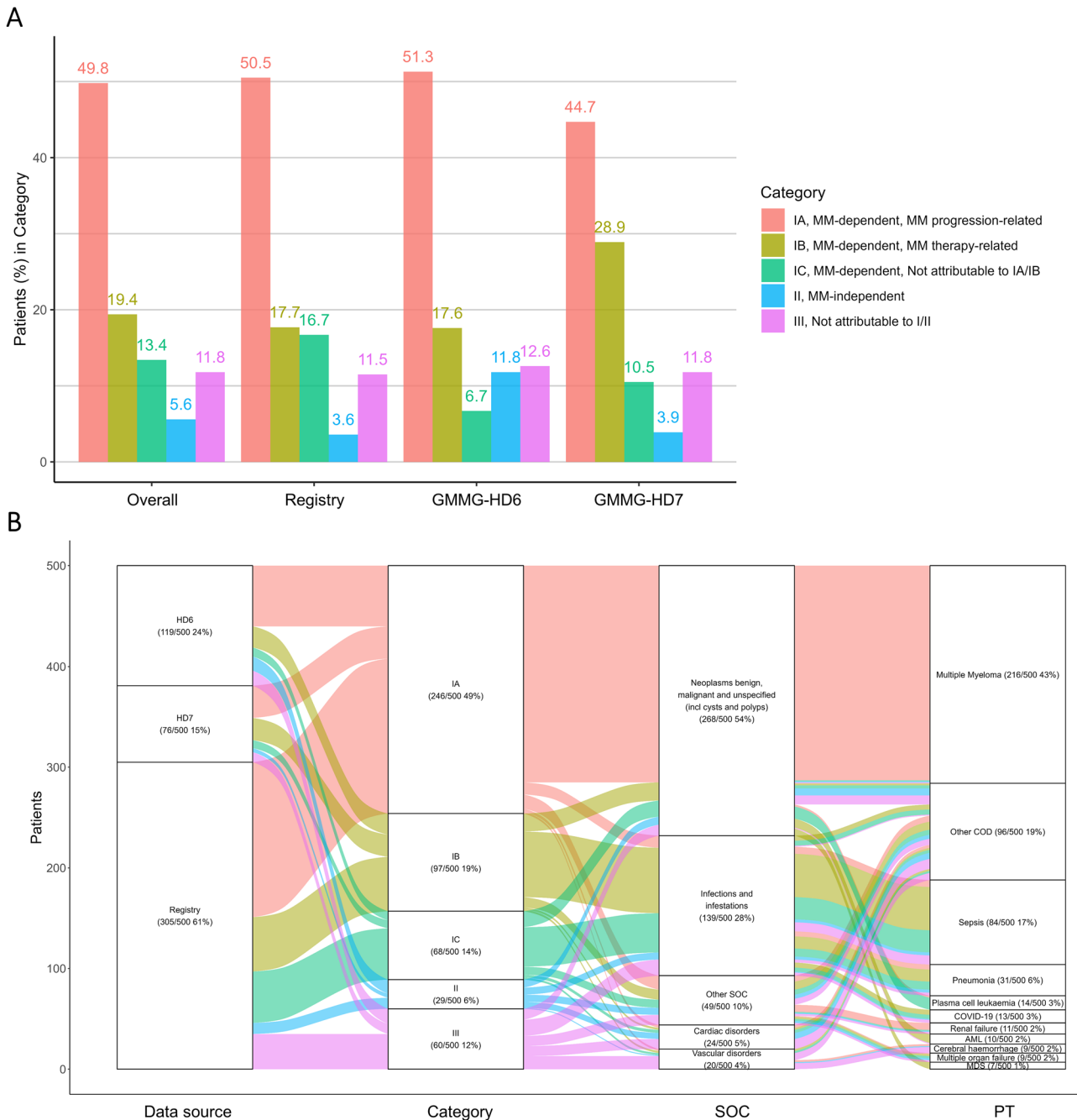
## RESULTS

Within known COD (81%, n = 500/617), we observed comparable trends across monocentric (Heidelberg-MM-registry) [7] and multicentric (GMMG-HD6/-HD7) [8–10] data (Fig. 1A). Overall, 413/500 (83%) patients died due to (I) MM-dependent causes: primarily MM-related: 249/500 (50%, IA), MM-therapy-related: 97/500 (19%, IB), and not attributable to (IA)/(IB): 67/500 (13%, IC). Comparatively, the GMMG-HD7 study which recruited and treated participants during the COVID-19 pandemic saw a notable rise of (IB) therapy-associated COD with 5/76 (6.6%) directly COVID-19-related (Supp. Fig. S1, Fig. 1B). IA mostly comprised MM-progression events, while IB/IC consisted largely of infection-related COD (Fig. 1B).

Over time, we observed fluctuating death counts peaking ~2019/2020 (Supp. Fig. S2A) while death counts by survival time peaked at around three years with otherwise similar distributions (Supp. Fig. S2B). IA comprised 24% of patients with survival less than half a year. Beyond that, IA accounted for ~43–58% of cases. The percentage of IB peaked during the initial years after therapy start (21–29%), decreasing with increasing survival (8–17%) (Supp. Fig. S2B). Further, IB showed a notable rise in infections ~2020, consisting mainly of COVID-19, pneumonia and sepsis (Supp. Fig. S3). Overall, 38/500 (8%) patients died to neoplastic causes other

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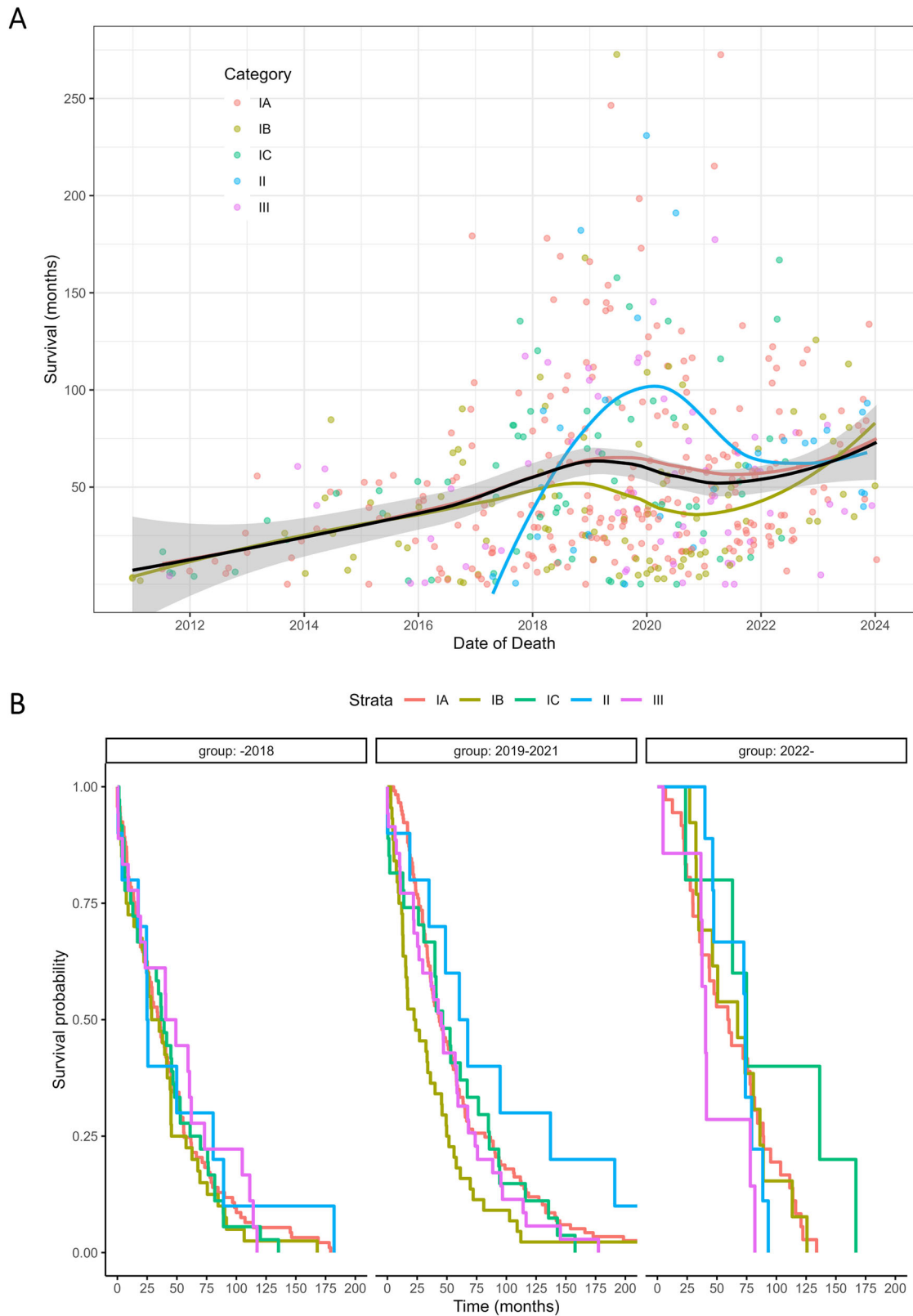
**Fig. 1 Global distribution of causes of death. A** Bar plot showing the percentage distributions of overall categories grouped by data sources. **B** Flow plot showing the distribution of patient COD categories ( $n = 500$ ).

than MM and plasma cell leukaemia. Therapy-associated SPM deaths consisted mainly of AML (10/38, 26%) and MDS (7/38, 18%) making up an increasing proportion of IB with increasing survival (Supp. Fig. S4). Hematological entities (ALL, AML, MDS, lymphoma) made up the majority (19/38, 50%) of SPM while remaining SPM included gastrointestinal (9/38, 24%), gynecological (4/38, 11%) and lung tumors (2/38, 5%) alongside other single-case solid tumors.

Regression analysis (Fig. 2A) showed a trend for increasing survival (black line) with notable downward trajectories around the COVID-19 pandemic (2019–2021), mostly driven by IB, mirroring leading COD trends in this timeframe [12]. Moreover, Kaplan-Meier survival analysis and COX modeling showed a significant difference between IA/IB (HR: 0.75, 95% CI: 0.59–0.95),

and II/IB (HR: 0.57, 95% CI: 0.38–0.86), mostly driven by infection-related IB between 2019 and 2021. Within this initial COVID-19 period, IB was associated with significantly decreased survival when compared to IA and II (Fig. 2B). Loess-regression-fitted survival times by year started with 24 (95%-CI:  $\pm 10$ ) months in 2014, reaching a local maximum in 2019 with 63 (95%-CI:  $\pm 7$ ) months. The pandemic-associated downward trend showed a local minimum at  $\sim 2021$  with 52 (95%-CI:  $\pm 7$ ) months where total survival at death started rising again, reaching 72 (95%-CI:  $\pm 18$ ) months in 2024.

Competing, cumulative risk for IB deaths exceeded IA around the period of half a year from the start of therapy (Supp. Fig. S5A). This increased risk trend is also mirrored in the SOC and COD: Here, cumulative risk of death associated with infections exceeded



**Fig. 2 Survival trends by category.** **A** Scatterplot of death date against total survival time (from start of therapy to death) with loess regression curves and 95% confidence intervals for the overall trend (black line). **B** Kaplan Meyer survival plots of categories IA, IB and II grouped by timeframe of death.

neoplasms during the initial year of therapy (Supp. Fig. S5B) while sepsis-related risks exceeded MM in about the same period (Supp. Fig. S5C).

In summary, we show that MM-progression-related events (about 50%) continue to make up the majority of COD, infections remain especially relevant within the first year after therapy initiation, and the COVID-19 pandemic led to a remarkable decrease in survival that has only recently returned to pre-pandemic rates.

## DISCUSSION

This study incorporated data from over a decade of MM treatment from two large multicentre phase 3 trials and a tertiary MM center, demonstrating similar COD distributions across time, comprising mainly primarily MM-associated deaths (43% MM-disease and 28% infections), comparable to previously observed trends [6, 7]. While absolute death count trends per COD are not directly interpretable due to fluctuating numbers of MM patients included per year, overall survival trends show an increasing trajectory. As our data only captured death data, surviving patients were not considered, potentially leading to an underestimation of true survival rates. Death counts peaking around 2020 may be attributable to the irregularly distributed initiation of therapy studies and the COVID-19 pandemic leading to an increased death toll [13]. Furthermore, as this study is based on German patients mostly, initially presenting at university hospitals, conclusions may not be directly translatable to low- and middle-income countries where many state-of-the-art therapeutic regimens may be less accessible. These regions may face a higher burden of directly myeloma-related death.

Since 2013, several new drugs entered MM treatment, including proteasome inhibitors (e.g., bortezomib or carfilzomib), monoclonal antibodies (e.g., daratumumab or isatuximab), and immunomodulatory drugs (e.g., lenalidomide and pomalidomide), exhibiting high response rates even as later line therapies [3–5]. Additionally, the definition and risk stratification criteria for MM [14] and smoldering MM [15] as essential grounds for therapeutic considerations have been consistently evolving, potentially contributing to a lead-time-bias.

Similar to other classification systems for COD, the MedDRA system oftentimes does not allow unique COD to SOC matching. This problem has also been observed for comparable classification systems [6] and has led to potentially obscured COD trends. As infections are known to greatly influence survival in MM patients, we assigned COD preferentially to the SOC “Infections and Infestations” in ambiguous cases. Similarly, malignancies were assigned to neoplasms over organ system of origin.

Interestingly, we observed that the survival time of IB patients was only significantly decreased for patients who died between 2019 and 2021, reflecting global COVID-19 incidence and mortality trends [13], potentially indicating that COVID-19 prophylaxis and immunization efforts for MM patients have since grown effective enough to restore survival to pre-pandemic rates. Despite only occurring from 2020–2022, directly COVID-19 related COD entered the top-5, at around 3% of all known COD. Of the other infection-related COD that saw a rise in frequency around the same time, some may nevertheless be COVID-19-associated due to factors such as missed diagnosis or multifactorial contribution to death. The heightened cumulative risk for death as a result of category IB and/or infection-related COD during the initial year of therapy further suggests a lower threshold for anti-infective therapy in this time period.

Collectively, our data demonstrates that while average patient survival continues to improve, the majority of MM patients still die due to MM and MM-related complications. This observation cements the fact that while the therapeutic spectrum for MM continues to expand, it largely remains an incurable disease with a

high rate of disease-associated mortality. SPM, primarily of hematological origin, constitute a therapy-related clinical concern that make up a notable but comparably small subgroup within therapy-related COD (8%). This finding should be considered in clinical practice. The remarkable impact of the COVID-19 pandemic on survival times further illustrates that MM patients remain highly susceptible to particularly novel types of infections [13].

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## DATA AVAILABILITY

Source data is available upon reasonable request to and decision of the corresponding author and the board of directors of the GMMG.

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## AUTHOR CONTRIBUTIONS

The conception and design of this study were done by JJ and EKM. JJ, BB, MHä, RF, UB, CH, IWB, CM, CS, RS, IvM, MH, EMK, MH, CL, HR, UMM, CSM, CK, ES, DG, TAWH, KTG, KCW, MSR, HJS, HG and EKM provided study material and patients. JJ, BB, MHä, RF, UB, CH, IWB, CM, CS, RS, IvM, MH, EMK, MH, CL, HR, UMM, CSM, CK, ES, DG, TAWH, KTG, KCW, MSR, HJS, HG and EKM treated patients within clinical trials and at the Heidelberg Myeloma Center. JJ, BY, UB, KJG, HG and EKM contributed to data collection and assembly. JJ, BY, UB, KJG, EMK, and EKM reviewed and assigned COD and categories. Administrative support was provided by UB, MSR, CMT, HG and EKM. JJ performed data cleaning and visualization. JJ and EKM analysed and interpreted the data. First draft of the manuscript was written by JJ and EKM. Interpretation and discussion of results, manuscript editing, further writing and final approval of the manuscript was done by all authors.

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## COMPETING INTERESTS

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## ADDITIONAL INFORMATION

**Supplementary information** The online version contains supplementary material available at <https://doi.org/10.1038/s41408-025-01380-z>.

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