Ageing and immunity: unraveling the association between immunosenescence and frailty

Tran Van Hoi, E.

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Toxicity in older cancer patients receiving immunotherapy – an observational study

Estelle Tran Van Hoi, Stella Trompet, Yara Van Holstein, Frederiek Van Den Bos, Diana Van Heemst, Henrik Codrington, Geert Labots, Suzanne Lohman, Asli Ozkan, Johanneke Portielje, Simon P. Mooijaart, Nienke A. De Glas, Marloes Derks

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ABSTRACT

Background

Immunotherapy by checkpoint inhibition has been established as an effective treatment strategy for a variety of diseases affecting the care of all patients with cancer, including older adults. However, older cancer patients represent a heterogeneous group as they can vary widely in frailty, cognition and physical status.

Objective

This study aims to investigate the association between clinical frailty and immune-related treatment toxicity (IrTox), hospitalization and treatment discontinuation due to IrTox in older patients treated with checkpoint inhibitors.

Patients and Methods

Patients aged 70 years and older, treated with checkpoint inhibitors, were selected from the TENT study, IMAGINE study and "Tolerability and safety of immunotherapy study". Clinical Frailty was assessed by Geriatric-8 (G8) score and WHO status. Outcomes were grades 3-5 toxicity, hospitalization and treatment discontinuation due to toxicity during treatment.

Results

Of the 99 patients included, 22% had comorbidities. While 33% of the patients were considered frail based on an abnormal G8 score of < 15, physical impairments were considered absent in 51% (WHO score of 0) and mild in 40% (WHO score of 1). Despite the limited sample size of the cohort, consistent trends were observed with patients with an abnormal G8 score of < 15 or higher WHO score of 1 for having higher odds of toxicity (OR 2.32 (95% 0.41-13.02); OR 1.33 (95% 0.45-4.17)), treatment discontinuation due to IrTox (OR 2.25 (95% 0.61-8.31); OR 2.18 (95% 0.7-6.73)); and hospitalization due to IrTox (OR 3.72 (95% 0. 39-35.4); OR 1.31 (95% 0.35-4.9)). Moreover, in a sub-analysis, we observed that the treatment discontinuation due to IrTox occurred often in patients with a grades 1-2 toxicity as well.

Conclusion

Although not statistically significant, in older patients treated with immunotherapy in a real-life population with cancer, we observed consistent trends towards increased toxicity, hospitalization and treatment discontinuation with increasing frailty. Larger studies are needed to confirm these exploratory results. Moreover, older patients with lower toxicity grade 1-2 experienced early treatment discontinuation frequently, suggesting a lower tolerance of toxicity.

INTRODUCTION

Cancer is highly prevalent in old age, and it is estimated that 55% of new cases are diagnosed in people aged over 65 years (1). Older patients are a heterogeneous group with large variation in geriatric problems such as impaired cognitive and physical functioning, comorbid diseases, polypharmacy or frailty. Treatment selection for older patients with cancer can be challenging in the setting of various impairments. Balancing potential benefits of treatment, such as increased survival or reduction of symptoms against potential harms like adverse side effects or risk of complications) can be difficult as the varying complexity in health issues among older patients can affect the ability to endure toxic cancer treatments.

Geriatric deficits have been associated with increased risk of toxicity due to chemotherapy, and with increased mortality (2, 3). Moreover, in the GAP-70 and GAIN randomized control trials, it was demonstrated that when treatment decisions were based on geriatric assessment (GA), toxicity was decreased due to dose reduction, while survival was unaffected, thereby supporting the implementation of GA-guided processes for cancer treatment (4-6). Therefore, a personalized treatment plan adjusted to the specific geriatric characteristics could lead to improved treatment care.

Immunotherapy with immune checkpoint inhibitors (ICI) has recently become a promising treatment for various types of cancer. For patients with advanced lung cancer, immunotherapy has improved overall survival with an acceptable toxicity profile (7). The most frequently used immunotherapies are pembrolizumab and nivolumab, which both target the programmed cell death protein 1 (PD-1) (8, 9). However, immunotherapy can have important side effects that may limit the ability to endure this treatment, especially in patients with additional geriatric deficits, considering the ageing immune system (10, 11). As prior studies showed no difference in the efficacy and toxicity of ICI based on calendar age, investigating frailty seems relevant. However, data on outcomes of immunotherapy in older people and their association with frailty are very scarce. For instance, Bruijnen et al. demonstrated that frail patients had higher irAE-related hospitalizations, longer stays, and more ICI discontinuations. Few studies demonstrated that geriatric impairments may increase the risk of immune-related adverse events in older patients treated with ICIs; however, association did not reach statistical significance (12, 13).

Therefore, the aim of the present study is to investigate the association between clinical frailty, measured by G8 score and WHO status, and treatment toxicity, hospitalization and treatment discontinuation due to toxicity in older patients treated with immunotherapy in a real-life population with cancer.

METHODS

Study population

For the present analyses, we selected patients from three ongoing studies: 1) TENT study, 2) IMAGINE study, 3) "Tolerability and safety of immunotherapy study", as described below. Patients were included between June 2011 and October 2020. We included patients with cancer of 70 years and older who were treated with immunotherapy regardless of treatment line and duration. Patients could be included both if they received only immunotherapy, the combination of immunotherapy and chemotherapy or the combination of immunotherapy and targeted therapy. All patients that were included in this cohort were treated in the Hagaziekenhuis (Den Haag, The Netherlands) or the Leiden University Medical Center (LUMC; Leiden, The Netherlands).

The Triage of Elderly Needing Treatment (TENT) study is a multicenter prospective study (14). All patients aged 70 years and older presenting in the outpatient department and needing an invasive medical intervention or treatment (surgery, chemotherapy or radiotherapy) in one of the participating hospitals undergo a short geriatric screening before their intervention. Prior to an invasive medical intervention, patients underwent a geriatric screening with the Geriatric-eight (G8) test and the 6-item Cognitive Impairment Test (6-CIT). Patients who scored abnormally on at least one of the two screening instruments received a comprehensive geriatric assessment (CGA) before starting treatment. The CGA is used to assess frailty or vulnerability in older patients, a clinical state characterized by a decline in functioning across multiple physiological systems, accompanied by increased vulnerability to stressors resulting in high risk of adverse health outcomes and mortality. CGA is a multidimensional assessment that takes into account medical diagnoses, psychological, somatic and functional impairments and social issues affecting patients' well-being (15). During follow-up, patients were assessed on mobility, independence and patients' self-rated health, mortality, toxicity and hospitalization. Participating patients were followed for 12 months and reassessed at 6 months and 12 months after the start of treatment. Ethical approval and consent to participate in the TENT study protocol were approved by the Medical Ethics Committee (METC) at Leiden University Medical Center. All participants or a proxy provided written informed consent.

The IMAGINE study (IMmunotherapy in AGINg patiEnts) is a prospective cohort study in patients who were treated in the LUMC with immunotherapy. Geriatric characteristics were gathered during the CGA and patients were followed over 24 months. Outcomes, including toxicity and hospitalization, were prospectively registered from medical charts. Ethics approval and consent to participate in The IMAGINE study protocol

were approved by the Medical Ethics Committee (METC) at Leiden University Medical Center. All participants or a proxy provided written informed consent.

The Tolerability and safety of immunotherapy study (ImToSa) is a partly retrospective cohort study; some patients were included after treatment, and others before treatment. All patients treated with immunotherapy were included in our study population. In the majority of patients, the G8 was performed as part of the standard of care. The initial aim of the study was to assess age-related differences in side-effects and predictors of toxicity, including gender, geriatric characteristics, and previous treatments. Patients were followed for 24 months. The METC Southwest Holland has issued that the study was not subject to Medical Research Involving Human Subjects Act (WMO) declaration. Patients consent was therefore not requested.

Clinical parameters

Tumor-specific information was extracted from the medical record or pathology report and consisted

of tumor type and tumor stage, which we eventually stratified into advanced or metastatic cancer.

Baseline parameters

For all 3 studies, demographic information was collected at baseline within 3 months before starting immunotherapy, including age, sex and living situation. Additionally, history of smoking and WHO performance score were assessed. The WHO performance score is classified with a score between 0 and 5, in which a higher score indicates a lower physical performance. A WHO score of 0 corresponds with an asymptomatic, fully active patient, a score of 1 corresponds to a symptomatic but ambulatory patient who can do light physical work, a score of 2 corresponds to a symptomatic patient that is <50% in bed during the day, and fully capable of self-care, a score of 3 corresponds to a symptomatic patient that is >50% in bed and capable of limited self-care, a score of 4 corresponds to a bedbound patient who is not able to perform any self-care and a score of 5 corresponds to a diseased patient (16) . The WHO status was extracted from the medical record.

Geriatric parameters

In the present study, we mainly focus on frailty using the G8 questionnaire, which was recorded before the start of treatment in all patients. The Geriatric-8 (G8) questionnaire is a frailty screening instrument and is used to assess if a CGA is further needed in older cancer patients. A G8 score < 15 (also “abnormal”) is considered to be potentially frail.

The presence of comorbidities was assessed. Comorbidities present at the time of diagnosis were classified into the following categories: 1) cardiovascular disease, 2) chronic lung disease, 3) neuropsychiatric, 4) rheumatoid arthritis, 5) ulcer, 6) other malignancy, 7) diabetes mellitus.

Outcomes

Endpoints were (i) immunotherapy-related toxicity (IrTox), (ii) hospitalization and (iii) treatment discontinuation due to toxicity. Severe toxicity was defined as grades 3 or higher immunotherapy-related side-effects according to the CTCAE criteria version 5 (17). In order to investigate the combined impact of treatment toxicity in (frail) older adults, we further defined "disadvantageous outcome" as having ≥1 of the 3 outcomes (IrTox, hospitalization and treatment discontinuation due to toxicity).

While the TENT and IMAGINE cohorts only included grade ≥3 toxicity, the Tolerability and Safety of Immunotherapy Study registered the full range of toxicity, including lower grades (grades 1-5). We performed a sub-analysis of associations between geriatric characteristics, all grades of toxicity and outcomes (immunotherapy-related toxicity, hospitalization and treatment discontinuation due to toxicity) in the Tolerability and Safety of Immunotherapy Study.

Data management

Data was recorded on Case Record Forms, encrypted, and stored in an electronic data management system (Castor EDC), in accordance with General Data Protection Regulations (GDPR).

Statistical analysis

Normal and skewed distributed continuous data were presented as respectively mean with standard deviation (SD) and median with interquartile range (IQR). Numbers with percentages were used to present categorical data. To investigate the association between baseline geriatric characteristics and toxicity, hospitalization and treatment discontinuation due to toxicity, we used a logistic regression model. Due to the relatively small number of events, we decided to perform univariate analyses only in order to avoid overfitting. Odds ratios with 95% confidence intervals (CI) were calculated, and a P-value of <0.05 was considered significant. All analyses were performed using SPSS (IBM version 25). All figures were graphically depicted using Microsoft Excel version 2019.

RESULTS

A total of 99 patients were included in this study: 21 from the TENT study, 68 from the ImToSa study and 10 from the IMAGINE study. Median follow-up was 15.8 months (IQR 11.2-20.4).

Patient characteristics are described in Table 1. We included 56 male patients and 43 female patients with a median age of 74 years (IQR 71.0-77.0 years). All patients had either stage III (advanced) or stage IV (metastatic) disease. Patients presented with lung cancer (71%), melanoma (11%), renal cell carcinoma (4%), breast cancer (8%) or urothelial cancer (6%). In the patient population with lung cancer, 39% had >50% PD-L1 expression. All patients were treated with immunotherapy, either as monotherapy (75%) or in combination with chemotherapy (19%) or targeted therapy (n=5, 5%). The majority of patients received either pembrolizumab (50%) or nivolumab (27%). Of all patients, 33% had an abnormal G8, 28% patients had a normal G8, and for 38% patients G8 score was not known. 78% of the patients had one or more comorbidities, 57% of whom had cardiovascular and 21% diabetes mellitus related.

Grade ≥3 toxicity outcomes

Types of grades ≥ 3 toxicity are presented in Figure 1. We observed 14% patients with Grade ≥3 toxicity due to immunotherapy. The most frequently observed types of toxicity were rash (18%) and pneumonitis (17%).

Hospitalization due to toxicity was seen in 10% of patients, and 21% of patients did not continue their treatment due to all-grade toxicity (Table 2).

Table 1. Patient and geriatric characteristics at baseline (N=99)

	N	%
Age (years), median (IQR)	99	74.0 (71.0-77.0)
Gender		
Male	56	56.6
BMI (median, IQR)	99	24.5 (22.3-27.1)
Healthy weight (18.5-24.9)	52	52.5
Underweight (<18.5)	7	7.1
Overweight (25-29.9)	31	31.3
Obese (>30)	9	9.1
History of smoking		
Yes	69	69.7
No	10	10.1
Unknown	20	20.2
Tumor type		
Non-small cell Lung carcinoma	70	70.7
Melanoma	11	11.1
Renal carcinoma	4	4.0
Urothelial carcinoma	6	6.1
Breast carcinoma	8	8.1
Tumor stage		
Locally Advanced	13	13.1
Metastatic	77	77.8
Unknown	9	9.1
Treatment		
Immunotherapy	75	75.8
Immuno- and chemotherapy	19	19.2
Immuno- and targeted therapy	5	5.1
Type of immunotherapy		
Ipilimumab	5	5.1
Nivolumab	27	27.3
Pembrolizumab	49	49.5
Atezolizumab	11	11.1
Durvalumab	6	6.1
Other	1	1.0

	N	%
G8 score		
Normal	28	28.3
Abnormal (< 15)	33	33.3
Unknown	38	38.4
WHO score		
Score 0	51	51.5
Score 1	40	40.4
Score 2-3	4	4.0
Unknown	4	4.0
Comorbidities		
Yes	77	77.8
No	22	22.2
Type of comorbidities		
Cardiovascular	56	56.6
Diabetes Mellitus	21	21.2
Asthma/COPD	21	21.2
Neuropsychiatric	4	4.0
Rheumatologic disease	3	3.0
Gastric ulcer	3	3.0
Other malignancy	11	11.1
More than 3 medications		
Yes	19	19.2
No	6	6.1
Unknown	74	74.7
Corticosteroids use[a]		
Yes	14	14.1
No	56	56.6
Unknown	29	29.3

[a] *In patients with grade III-V toxicity*

Abbreviations: N, number of patients; BMI, body mass index; COPD, chronic obstructive pulmonary disorder; G8, Geriatric-8 test; IQR, interquartile range; WHO score, Eastern Cooperative Oncology Group (ECOG) score

Table 2. Hospitalization and treatment discontinuation

	N	%
Hospitalization due to toxicity		
Yes	10	10.1
No	89	89.9
Treatment discontinuation		
Yes	78	78.8
No	19	19.2
Unknown	2	2.0
Treatment discontinuation reason (N=78)		
Due to toxicity	16	20.5
Due to severe toxicity (grade 3-5)	6	7.6
Due to disease progression	40	51.2
Other	22	28.2

Abbreviations: N, number of patients

Figure 1. Incidence of toxicity and types of toxicity (grade 3-5)

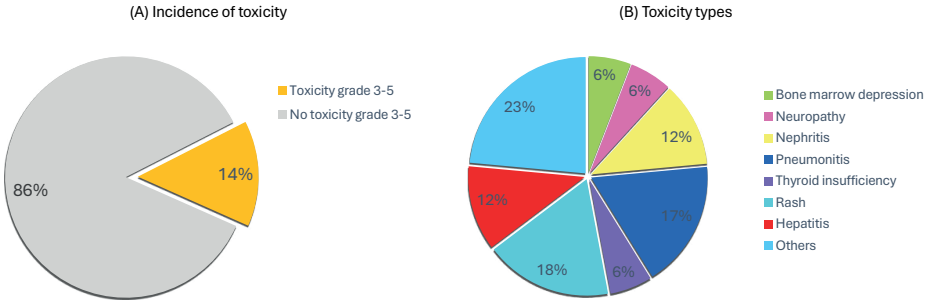

Figure 1. (A) Pie chart describing the incidence of toxicity grade 3-5. (B) Pie chart describing the toxicity types among patients with toxicity grade 3-5.

Results of the univariate analysis of toxicity are described in Table 3A, 3B. Although none of the associations with grade ≥ 3 toxicity were statistically significant, observed effect estimates showed consistent directions of effect as described below. Higher risk of Grade ≥*3* toxicity tended to be positively associated with higher age (OR 1.07 (95% 0.95-1.21)) and being overweight (OR 2.74 (95% 0.79-9.56)). As per treatment type, patients receiving immune- and chemotherapy showed a tendency towards higher risk of Grade ≥3 toxicity (OR 2.62 (95% 0.72-9.01)) compared to patients receiving immunotherapy alone. A tendency towards increased risk of toxicity

was observed in patients with an abnormal G8 score of < 15 (OR 2.32 (95% 0.41-13.02)) and a higher WHO score of 1 (OR 1.33 (95% 0.43-4.17)). Moreover, increased comorbidities tended to be associated with increased risk of toxicity (OR 1.85 (95% 0.38-9.0). The effect estimates were highest for cardiovascular comorbidities (OR 3.26 (95% 0.85-12.52)) and diabetes (OR 1.6 (95% 0.45-5.73)).

Comparable results were observed for treatment discontinuation and hospitalization due to toxicity (supplementary table 2-3).

Figure 2 reports the overlap of toxicity risk, treatment discontinuation and hospitalization due to IrTox. All patients who were hospitalized had toxicity and/or discontinued their treatments.

Figure S1 reports the incidence of comorbidity in patients with ≥ 1 disadvantageous outcome. 25% of the patients (n=24) had ≥1 disadvantageous outcome (toxicity grade ≥3 or hospitalization due to IrTox or treatment discontinuation due to IrTox). Of the patients with comorbidities (n=77), 29% (n=22) had ≥1 disadvantageous outcome, while of the patients without comorbidities (n=22), 9% (n=2) had ≥1 disadvantageous outcome.

Table 3. Determinants of toxicity risk (grade 3-5)

(A)		N	N events	OR	95% CI		p-value
					Lower	Upper	
Age		99	14	1.073	0.952	1.208	0.248
BMI							
	Healthy weight (18.5-24.9)	52	5	Reference			
	Underweight (<18.5)	7	1	1.567	0.156	15.768	0.703
	Overweight (25-29.9)	31	7	2.742	0.787	9.555	0.113
	Obese (>30)	9	1	1.175	0.121	11.420	0.889
Tumor type							
	Breast cancer	8	1	Reference			
	Non-small cell lung cancer	70	8	0.903	0.098	8.324	0.928
	Melanoma	11	5	5.833	0.525	64.823	0.151
	Renal carcinoma	4	0	NA			
	Urothelial carcinoma	6	0	NA			
Treatment type							
	Immunotherapy	75	9	reference			
	Immuno- and chemotherapy	19	5	2.619	0.716	9.014	0.127
	Immuno- and targeted therapy	5	0	NA			
Type of immunotherapy							
	Pembrolizumab	49	7	Reference			
	Nivolumab	27	4	1.043	0.276	3.944	0.95
	Ipilimumab	5	2	4.0	0.563	28.396	0.166
	Atezolizumab	11	1	0.6	0.066	5.447	0.650
	Durvalumab	6	0	NA			
	Other	1	0	NA			

(B)	N	N events	OR	95% CI		p-value
				Lower	Upper	
G8 score						
Normal	28	2	reference			
Abnormal (< 15)	33	5	2.321	0.414	13.023	0.338
Unknown	38	7	2.935	0.561	15.372	0.202
WHO score						
Score 0	51	7	reference			
Score 1	40	7	1.333	0.426	4.172	0.621
Score 2-3	4	0	NA			
Unknown	4	0	NA			
Comorbidities						
No	22	2	reference			
Yes	77	12	1.846	0.381	8.951	0.447
Type of comorbidities						
Cardiovascular	56	11	3.259	0.849	12.519	0.085
Diabetes Mellitus	21	4	1.6	0.447	5.729	0.470
Asthma/COPD	21	2	0.579	0.119	2.815	0.498
Neuropsychiatric	4	1	2.103	0.203	21.774	0.533
Rheumatologic disease	3	0	NA			
Gastric ulcer	3	0	NA			
Other malignancy	11	0	NA			

Abbreviations: N, number of patients; N events, number of patients with toxicity; OR, odds ratio for univariable logistic regression; BMI, body mass index; COPD, chronic obstructive pulmonary disorder; G8, Geriatric-8 test; WHO score, Eastern Cooperative Oncology Group (ECOG) score; NA, not applicable

Figure 2. Overlap of toxicity risk, treatment discontinuation and hospitalization due to IrTox.

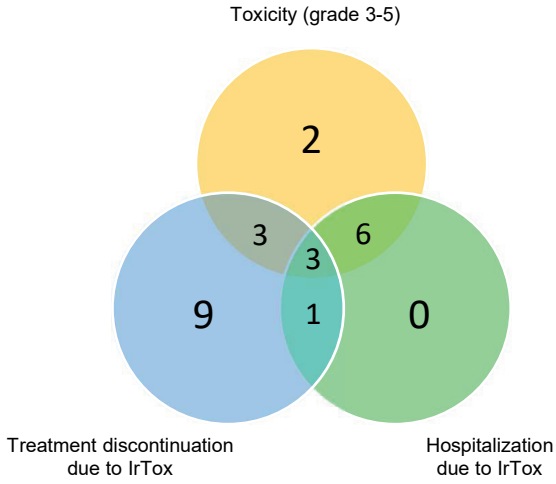

Figure 2. Venn Diagram describing the overlap of the different disadvantageous outcomes due to IrTox: risk of severe toxicity (grade 3-5), treatment discontinuation due to IrTox and hospitalization due to IrTox.

All grade toxicity in the Tolerability and Safety of Immunotherapy study

Figure 3 reports the incidence of all grades of toxicity and types of toxicity in the sub-analysis of the Tolerability and Safety of Immunotherapy study. Patient characteristics are described in Supplementary Table 3. Included patients (n=68) had a median age of 75 years (IQR 71.0-77.0 years). Most patients had lung cancer (n=53, 78%). All patients were treated with immunotherapy, either as monotherapy (n=62, 91%) or in combination with chemotherapy (n=6, 9%); the majority of patients received either pembrolizumab (n=30, 44%) or nivolumab (n=25, 37%). 38.2% patients had a G8 < 15, 22% patients had a G8>14 and for 40% patients, G8 score was not known.

Of the group of 68 patients, 81% of all patients had toxicity (any grade). Of these, 68% of toxicities were grade 1, 49% grade 2 and 9% grade 3. Fatigue (24%), rash (21%) and pruritis (17%) were the most common types of toxicity. In this subgroup, 9% of the patients have been hospitalized due to toxicity, and 16% of the patients had a treatment discontinuation due to toxicity (Table 4). Results of the univariable analysis of toxicity of the sub-cohort did not show predictors for toxicity (Supplementary Table 4).

Figure 3. Incidence of toxicity and toxicity types in the Tolerability and Safety of Immunotherapy study (N=68)

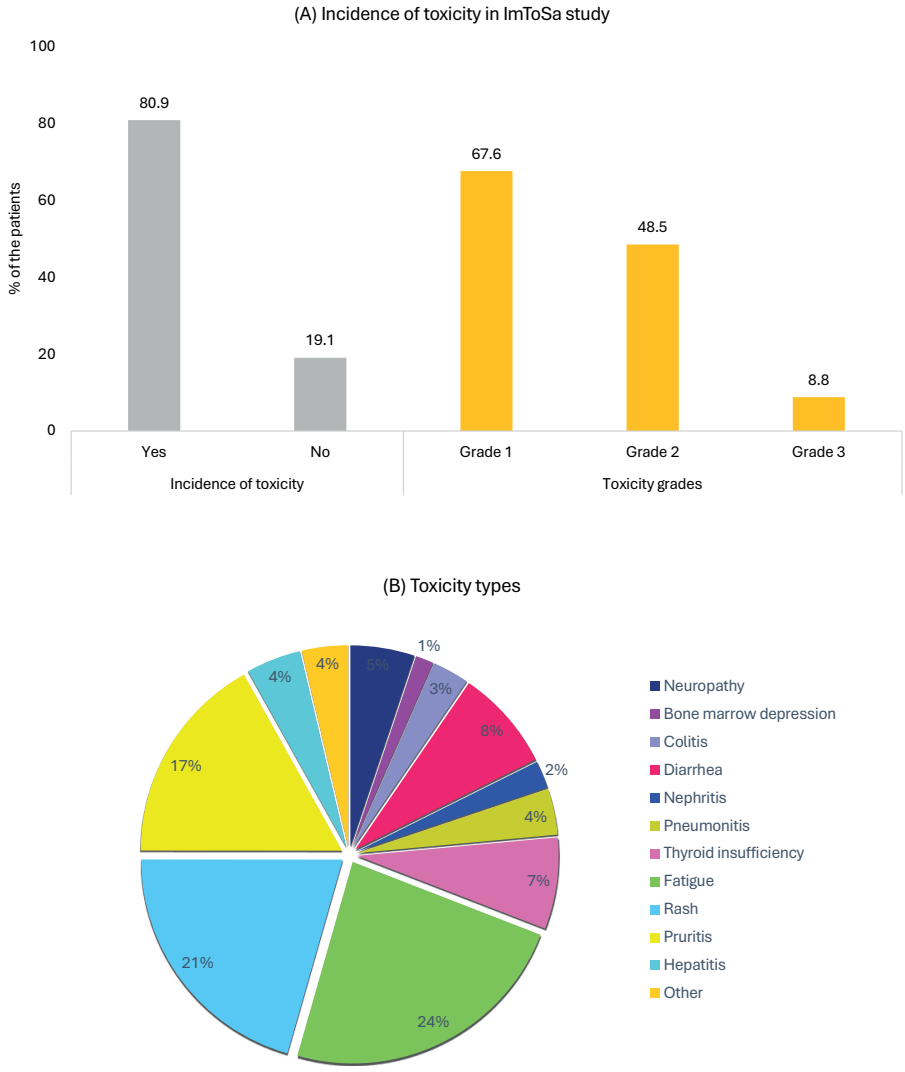

Figure 3. (A) Graphic describing the incidence of all grades of toxicity and the incidence of each grade of toxicity. (B) Pie chart describing toxicity type in patients with all grade toxicity.

Table 4. Incidence of hospitalization and treatment discontinuation due to toxicity (grade 1-5) in the ImToSa study

	N	%
Hospitalization due to toxicity		
Yes	6	8.8
No	62	91.2
Corticosteroids use		
Yes	10	14.7
No	50	73.5
Unknown	8	11.8
Treatment discontinuation		
Yes	54	79.4
No	14	20.6
Unknown		
Treatment discontinuation reason		
Due to toxicity (grade 1-5)	11	16.2
Due to disease progression	26	38.2
Other	17	25
Total	54	79.4
Missing	14	20.6

Abbreviations: N, number of patients

DISCUSSION

The present study observed consistent trends towards increased toxicity-related outcomes with frailty measured by the G8 score and comorbidities, although none of the observed associations were statistically significant. Both an abnormal G8 score of < 15 and a higher WHO score of 1 tended to be associated with a higher risk of toxicity, hospitalization, and treatment discontinuation due to toxicity. Additionally, severe toxicity tended to be more prevalent in patients with comorbidities, especially with cardiovascular comorbidities. Association of comorbidities showed trends towards higher odds of treatment discontinuation and hospitalization due to toxicity. Moreover, older frail patients were more at risk of experiencing a disadvantageous outcome. We observed that a considerable proportion of older patients had grade 1 or 2 toxicity with fatigue, rash and pruritis most often experienced. Of these patients, 16% discontinued treatment. These results suggest that grades 1 to 2 toxicities in older adults can lead to early immunotherapy discontinuation.

Numerous studies have confirmed the role of GA in predicting chemotherapy-related adverse events, but the association of frailty with ICI-related adverse events has not been extensively studied (18, 19). Bruijnen et al showed that significantly more frail patients were admitted to the hospital because of immune-related adverse events (irAEs) and, in addition, observed a trend toward increased length of hospitalization and ICI discontinuation for irAEs (20). Similarly, the ELDERS study demonstrated that an abnormal G8 score < 15 was a predictor of higher risk of irAEs such as comorbidity-related hospital admissions (p=0.031) and risk of death (p=0.01) (21). Comparable to our study, this suggests that lower-grade irAE in older patients may challenge tolerance due to comorbidity burden, reduced organ function and reduced reserve capacities. Less severe toxicities can obviously severely affect older patients in their daily functioning and quality of life. Moreover, a recent study revealed that higher comorbidity burden was associated with shorter overall survival (OS), suggesting that these conditions may limit the benefits of the treatment. Specifically, cardiovascular disease may predict shorter OS in patients experiencing irAEs (22), indicating the need for careful evaluation in this patient group. These findings align with our data, showing a trend toward immune-related toxicity in patients with comorbidities, especially with cardiovascular comorbidities. The present results highlight the importance of studies of patient-reported outcomes such as quality of life and functionality.

In randomized clinical trials, ICIs have been shown to have similar efficacy in older patients compared to younger patients with various types of cancer (23). In pivotal RCTs, however, only selected, more fit, older patients have participated, and little is known about the effects of ICI in older patients with frailty or comorbidities. Although initially proposed that checkpoint inhibitors could be less effective in

older patients due to ageing of the immune system (immunosenescence), this has never been demonstrated in real-world populations (24, 25). Activation of PD-1 results in decreased T cell effector activity, proliferation and survival, hence leading to an immunosuppressive function. When this immunosuppressive function is exploited by cancer cells, a tumor immune escape is enhanced. Therefore, the immunosenescence phenomenon may induce different efficacy and/or toxicity patterns of immunotherapies in older patients. Another concern is that older cancer patients may benefit less from immunotherapy because they are less resilient to endure toxic treatments (26, 27). This makes it even more important to incorporate predictive factors for toxicity in treatment decisions in older adults. Polypharmacy may serve as a significant predictive factor for toxicity in treatment decision-making. While our study did not examine polypharmacy due to limited data availability, it is critical to acknowledge its high prevalence in older cancer patients. Existing preliminary evidence demonstrates the correlation between polypharmacy and various health outcomes, such as adverse drug events, falls, frailty, hospitalization, postoperative complications, and mortality (28, 29). For instance, research by Hakozaki et al. in older patients with advanced non-small-cell lung cancer undergoing ICI therapy found an association between polypharmacy and an elevated rate of unexpected hospitalizations (30). Similarly, another study reported a high incidence of polypharmacy alongside increased rates of post-chemotherapy hospitalization. These studies collectively indicate that the concurrent use of multiple medications can significantly impact the treatment outcomes (31).

The main strengths of the present study include the incorporation of detailed toxicity outcome measures, including all-grade toxicity in the majority of the cohort. To the best of our knowledge, this is the first study that included all-grade toxicity and its consequences in relation to frailty. However, the study has several limitations in its scope and statistical power to detect significant associations. First, the most important limitation was the low sample size with low numbers of events, with substantial missing data. Second, this study included three different data sources (from two prospective studies and one partly retrospective study), affecting the uniformity of the results. Additionally, it can be noted that our study primarily focuses on a cohort with a significant representation of NSCLC, alongside other cancers. While our dataset comprises different tumor types, it is indeed weighted towards NSCLC. Nevertheless, our results suggesting a trend towards an association between frailty and immunotherapy toxicity are consistent with the current literature encompassing various forms of cancer (12). Moreover, our dataset lacked detailed information regarding pre-treatments that could have influenced the baseline characteristics of the patients and subsequent outcomes. Similarly, we did not have data on delirium, an increasing concern in older patients receiving immunotherapy.

Third, in the retrospective part of the ImTosa, one third of the patients had a missing G8-score, resulting in a lack of power of the study. Finally, we did not have data available of a full geriatric assessment, but were only able to study G8-score, comorbidity and WHO status as predictors of toxicity-related outcomes.

The present study supports the hypothesis of a possible association between frailty measured by the G8 and risk of immunotherapy toxicity, treatment discontinuation and hospitalization due to toxicity, but larger prospective real-life studies of patients are needed to confirm these results.

In conclusion, in patients treated with immunotherapy in a real-life population with cancer, we observed consistent trends towards increased toxicity, hospitalization and treatment discontinuation with increasing frailty, although not statistically significant (potentially) due to low numbers. Larger studies should be performed to confirm these associations. Moreover, many patients with lower toxicity grade 1-2 experienced early treatment discontinuation, suggesting a lower tolerance of toxicity in frail older patients.

DECLARATIONS

Funding

No external funding was used in the preparation of this manuscript.

Conflict of interest

Estelle Tran Van Hoi, Johanneke Portielje, Diana van Heemst, Nienke De Glas, Simon Mooijaart and Marloes Derks declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Code availability

Not applicable.

Data availability

Not applicable.

Authors contributions

S. Trompet, Y. Van Holstein, F. Van Den Bos contributed in the design and implementation of the TENT study. H. Codrington and G. Labots contributed in the implementation of the ImToSa study. A. Ozkan contributed to the patients follow-up and managed the IMAGINE study database. S. Lohman contributed in preparing the database of the present study. E. Tran Van Hoi carried the research and analysis with the supervision of N.A. De Glas, J. Portielje, S.P. Mooijaart and M. Derks. M. Derks conducted the present research.

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SUPPLEMENTARY MATERIAL

Table S1. Determinants of treatment discontinuation due to toxicity (TENT-IMAGINE-ImToSa study)

	N	N events	OR	95% CI		p-value
				Lower	Upper	
Age	99	17	0.991	0.879	1.117	0.878
BMI						
Healthy weight (18.5-24.9)	52	8	Reference			
Underweight (<18.5)	7	0	NA			
Overweight (25-29.9)	31	6	1.320	0.411	4.239	0.641
Obese (>30)	9	2	1.571	0.275	8.977	0.611
Tumor type						
Breast cancer	8	1	Reference			
Non-small cell lung cancer	70	13	1.596	0.180	14.125	0.674
Melanoma	11	2	1.556	0.116	20.854	0.739
Renal carcinoma	4	0	NA			
Urothelial carcinoma	6	0	NA			
Treatment type						
Immunotherapy	75	14	reference			
Immuno- and chemotherapy	19	2	0.513	0.106	2.479	0.406
Immuno- and targeted therapy	5	0	NA			
Type of immunotherapy						
Pembrolizumab	49	9	Reference			
Nivolumab	27	7	1.556	0.505	4.787	0.441
Ipilimumab	5	0	NA			
Atezolizumab	11	0	NA			
Durvalumab	6	0	NA			
Other	1	0	NA			
G8 score						
Normal	28	4	reference			
Abnormal (< 15)	33	9	2.250	0.609	8.311	0.224
Unknown	38	3	0.514	0.105	2.508	0.411

	N	N events	OR	95% CI		p-value
				Lower	Upper	
WHO score						
Score 0	51	6	reference			
Score 1	40	9	2.177	0.704	6.739	0.177
Score 2	3	0	NA			
Score 3	1	1	1.212	0		
Unknown	4	0	NA			
Comorbidities						
No	22	1	Reference			
Yes	77	15	5.081	0.632	40.825	0.126
Types of comorbidities						
Cardiovascular	56	13	4.031	1.069	15.198	0.04
Diabetes Mellitus	21	3	0.833	0.214	3.246	0.793
Asthma/COPD	22	2	0.481	0.1	2.307	0.36
Neuropsychiatric	4	0	NA			
Rheumatologic disease	3	1	2.7	0.230	31.694	0.429
Gastric ulcer	3	0	NA			
Other malignancy	11	2	1.175	0.229	6.026	0.847

Abbreviations: N, number of patients; N events, number of patients with toxicity; OR, odds ratio for univariable logistic regression; BMI, body mass index; COPD, chronic obstructive pulmonary disorder; G8, Geriatric-8 test; WHO score, Eastern Cooperative Oncology Group (ECOG) score; NA, not applicable

Table S2. Determinants of hospitalization due to toxicity (TENT-IMAGINE-ImToSa study)

	N	N events	OR	95% CI		p-value
				Lower	Upper	
Age	99	10	0.994	0.859	1.1150	0.936
BMI						
Healthy weight (18.5-24.9)	52	3	Reference			
Underweight (<18.5)	7	0	NA			0.999
Overweight (25-29.9)	31	6	3.920	0.904	17.002	0.068
Obese (>30)	9	1	2.042	0.188	22.135	0.557
Tumor type						
Breast cancer	8	1	Reference			
Non-small cell lung cancer	70	6	0.656	0.069	0.069	0.714
Melanoma	11	3	2.625	0.220	31.349	0.446
Renal carcinoma	4	0	NA			
Urothelial carcinoma	6	0	NA			
Treatment type						
Immunotherapy	75	7	reference			
Immuno- and chemotherapy	19	3	1.821	0.424	7.828	0.420
Immuno- and targeted therapy	5	0	NA			
Type of immunotherapy						
Pembrolizumab	49	4	Reference			
Nivolumab	27	4	1.957	0.448	8.545	0.372
Ipilimumab	5	1	2.813	0.251	31.571	0.402
Atezolizumab	11	1	1.125	0.113	11.175	0.920
Durvalumab	6	0	NA			
Other	1	0	NA			
G8 score						
Normal	28	1	reference			
Abnormal (< 15)	33	4	3.724	0.391	35.444	0.253
Unknown	38	5	4.091	0.450	37.160	0.211
WHO score						
Score 0	51	5	reference			

	N	N events	OR	95% CI		p-value
				Lower	Upper	
Score 1	40	5	1.314	0.353	4.897	0.684
Score 2-3	4	0	NA			
Unknown	4	0	NA			
Comorbidities						
No	22	0	reference			
Yes	77	10	NA			
Types of comorbidities						
Cardiovascular	56	8	3.417	0.687	17.0	0.133
Diabetes Mellitus	21	3	1.690	0.397	7.192	0.477
Asthma/COPD	21	2	0.921	0.180	4.702	0.921
Neuropsychiatric	4	1	3.185	0.299	33.905	0.337
Rheumatologic disease	3	0	NA			
Gastric ulcer	3	0	NA			
Other malignancy	11	0	NA			

Abbreviations: N, number of patients; N events, number of patients with toxicity; OR, odds ratio for univariable logistic regression; BMI, body mass index; COPD, chronic obstructive pulmonary disorder; G8, Geriatric-8 test; WHO score, Eastern Cooperative Oncology Group (ECOG) score; NA, not applicable

Sub-analysis of the Tolerability and Safety of Immunotherapy study

Table S3. Patient and geriatric characteristics at baseline of the ImToSa study

	N	%
Age (years), median (IQR)	68	74.7 (71.0-77.0)
Gender		
Male	39	57.4
BMI (median, IQR)		
Healthy weight (18.5-24.9)	39	57.4
Underweight (<18.5)	4	5.9
Overweight (25-29.9)	19	27.9
Obese (>30)	6	8.8
History of smoking		
Yes	49	72.1
No	9	13.2
Unknown	10	14.7
Tumor type		
Non-small cell Lung carcinoma	53	77.9
Renal carcinoma	2	2.9
Urothelial carcinoma	5	7.2
Breast carcinoma	8	11.8
Tumor stage		
Locally Advanced	10	14.7
Metastatic	51	75
Unknown	7	10.3
Treatment		
Immunotherapy	62	91.2
Immuno- and chemotherapy	6	8.8
Type of immunotherapy		
Nivolumab	25	36.8
Pembrolizumab	30	44.1
Atezolizumab	9	13.2
Durvalumab	4	5.9
G8 score		
Normal	15	22.1
Abnormal (< 15)	26	38.2
Unknown	27	39.7

	N	%
WHO score		
Score 0	36	52.9
Score 1	28	41.2
Score 2-3	3	4.4
Unknown	1	1.5
Comorbidities		
Yes	59	86.8
No	9	13.2
Type of comorbidities		
Cardiovascular	44	64.7
Diabetes Mellitus	13	19.1
Asthma/COPD	20	29.4
Psychosocial disease	4	5.9
Rheumatologic disease	3	4.4
Gastric ulcer	2	2.9
Other malignancy	11	16.2

Abbreviations: N, number of patients; BMI, body mass index

Table S4. Determinants of toxicity risk in the ImToSa study

	N	N events	OR	95% CI		p-value
				Lower	Upper	
Age	68	55	0.861	0.742	0.998	0.048
BMI						
Healthy weight (18.5-24.9)	39	33	Reference			
Underweight (<18.5)	4	3	0.545	0.048	6.162	0.624
Overweight (25-29.9)	19	14	0.509	0.133	1.947	0.324
Obese (>30)	6	5	0.090	0.090	9.219	0.936
Tumor type						
Non-small cell Lung carcinoma	53	43	Reference			
Renal carcinoma	2	1	0.233	0.013	4.044	0.317
Urothelial carcinoma	5	3	0.349	0.051	2.372	0.282
Breast carcinoma	8	8	NA			
Treatment type						
Immunotherapy	62	50	Reference			
Immuno- and chemotherapy	6	5	1.2	0.128	11.245	0.873
Type of immunotherapy						
Pembrolizumab	30	22	Reference			
Nivolumab	25	20	1.455	0.408	5.184	0.563
Durvalumab	4	4	NA			
Atezolizumab	9	9	NA			
G8 score						
Normal	15	11	Reference			
Abnormal (< 15)	26	21	1.527	0.340	6.869	0.581
Unknown	27	23	2.091	0.439	9.961	0.354
WHO score						
Score 0	36	31	Reference			
Score 1	28	22	0.591	0.160	2.184	0.431
Score 2	2	0	NA			
Score 3	1	1	NA			
Unknown	1	1	NA			

	N	N events	OR	95% CI		p-value
				Lower	Upper	
Comorbidities						
No	9	9	Reference			
Yes	59	46	NA			
Types of comorbidities						
Cardiovascular	18	10	Reference			
Asthma/COPD	15	12	1.491	0.364	6.116	0.579
Psychosocial disease	4	4	NA			
Rheumatologic disease	3	3	NA			
Gastric Ulcer	1	1	NA			
Other malignancy	11	10	2.667	0.310	22.939	0.372
Diabetes Mellitus	7	6	1.375	0.265	7.125	0.704

Abbreviations: N, number of patients; N events, number of patients with toxicity; OR, odds ratio for univariable logistic regression; BMI, body mass index; COPD, chronic obstructive pulmonary disorder; G8, Geriatric-8 test; WHO score, Eastern Cooperative Oncology Group (ECOG) score; NA, not applicable

Figure S1. Incidence of comorbidity in patients with ≥ 1 disadvantageous outcome in the IMAGINE, TENT, ImToSa studies combined.

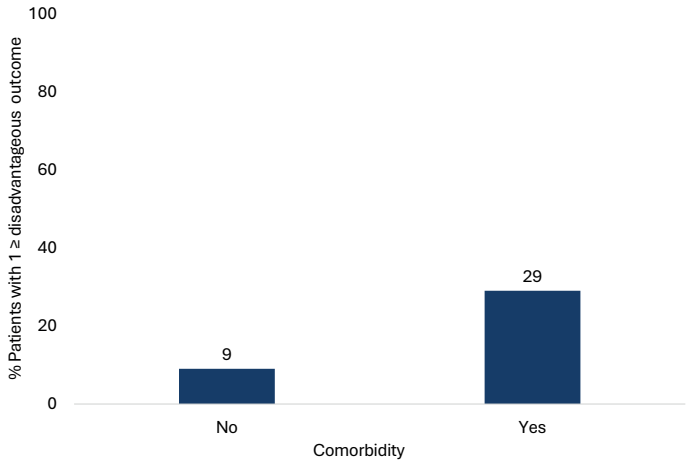

Figure S1. Graphic describing the incidence of comorbidity among patients with ≥ 1 disadvantageous outcome (toxicity risk, treatment discontinuation and hospitalization due to IrTox) in the IMAGINE, TENT, ImToSa studies combined.