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Research paper

Real-life safety of PD-1 and PD-L1 inhibitors in older patients with cancer: An observational study

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ABSTRACT

Introduction: To compare the real-world safety profile of programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) inhibitors between younger and older patients.

Materials and Methods: All patients receiving pembrolizumab, nivolumab, atezolizumab or durvalumab between September 2016 and September 2019 at Haga Teaching Hospital, The Hague, The Netherlands were included in this retrospective study. Immune-related adverse drug reactions (irADRs) were manually retrieved from the electronic patient files. The cumulative incidence of irADRs were compared between younger (<65 years) and older (≥65 years) patients using a Pearsons Chi-square test.

Results: We identified 217 patients who were treated with at least one dose of PD-(L)1 inhibitor. 58% were 65 years or older at the start of immunotherapy. 183 patients (84.3%) received monotherapy PD-(L)1 inhibitors and 34 (15.7%) received chemo-immunotherapy. A total of 278 irADRs were registered. Cutaneous irADRs (53.9%), thyroid gland disorders (20.3%), and non-infectious diarrhoea/colitis (17.5%) were the most frequently reported irADRs. The majority of the irADRs were mild to moderate and no fatal irADRs were observed. 61 (21.9%) of the irADRs needed systemic treatment, of which 19 (6.8%) required treatment with corticosteroids. 18 irADRs (6.5%) were severe and resulted in hospitalisation.

The cumulative incidence of cutaneous irADRs was different between the age groups: 45.7% of the patients <65 years and in 60.0% of the patients ≥65 years ($p = 0.036$). No statistical difference was found in the cumulative incidence of other irADRs between the two age groups.

Discussion: Advanced age is not associated with immune-related adverse drug reactions of PD-1 and PD-L1 inhibitors.

1. Introduction

Over the last decade, the development of immune checkpoint inhibitors (ICIs) has been one of the most important achievements in the treatment of cancer. The efficacy and safety of programmed cell death-1 (PD-1) inhibitors and programmed cell death ligand-1 (PD-L1) inhibitors have been widely explored in various clinical trials. Results suggest an improved progression-free survival (PFS) and overall survival (OS) in several patient populations including those with melanoma, non-small cell lung carcinoma (NSCLC), urethral cell carcinoma (UCC) and renal cell carcinoma (RCC). The safety profile of PD-1 and PD-L1 inhibitors appears to be more favourable when compared to cytotoxic chemotherapy agents [1–5]. However, ICIs are associated with a considerable risk of immune related adverse drug reactions (irADRs) [6–8].

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Due to the aging of society, the incidence rate of cancer in older patients is likely to increase in upcoming years. In spite of the current efforts to elucidate the effectiveness and safety of ICIs, our knowledge in special patient populations such as older patients remains limited due to their underrepresentation in clinical trials. Furthermore, older patients participating in trials are often fitter than older patients in clinical practice. The tumour types for which PD-1 and PD-L1 inhibitors are prescribed, predominantly affect older patients. Half of all lung cancer diagnoses occur in patients older than 70 years [9]. Moreover, aging is associated with immunosenescence, which could decrease the effectiveness of ICIs as well as the incidence of irADRs [10,11]. However, irADRs may be less well tolerated in older patients.

A number of post-marketing studies, including CheckMate 153, have investigated the effectiveness of ICIs in older patients. The findings of these studies are mainly consistent with the registration studies [12]. However, additional real-world-data (RWD) on the safety profile of PD-1 and PD-L1 inhibitors in older patients is needed to bridge the gap between the outcomes of clinical trials and clinical practice. To this end, we conducted a real-world observational study to compare the incidence and severity of immune-related adverse drug reactions (irADRs) in younger and older patients treated with PD-1 or PD-L1 inhibitors.

2. Methods

2.1. Study Design and Patient Population

A retrospective observational study was conducted in consecutive patients who started treatment with pembrolizumab, nivolumab, atezolizumab or durvalumab between September 2016 and September 2019 in Haga Teaching hospital, The Hague, The Netherlands. Patients who opted out of sharing their data for research purposes were excluded.

Data were manually retrieved from the 'Cytostatics Management System (CMS)' and Electronic Patient Files (EPFs). CMS contains data on patient treatment regimen, dosage, and administration of (chemo-) immunotherapy. The EPF contains data on patient demographics, health behaviour, vital signs, laboratory data, concomitant medications, procedures, imaging, health problem lists, and free-text notes of the healthcare professionals.

This research was approved by the Board of Directors of Haga Teaching hospital. The local Medical Ethical Review Committee (METC Leiden Den Haag Delft) granted a waiver for obtaining informed consent.

2.2. Data Collection

EPFs were retrospectively reviewed and data on baseline characteristics, malignancy type, PD-L1 status, Eastern Cooperative Oncology Group (ECOG) performance score at the beginning of therapy, polypharmacy, and comorbidities were collected. Concerning malignancy type, small cell lung carcinoma, Hodgkin's lymphoma and mamma carcinoma were classified as 'other'. PD-L1 expression of the tumour was classified as 'negative' (PD-L1 expression <1%), 'positive' (PD-L1 expression >1%) or 'strongly positive' (PD-L1-expression >50%). Only cardiovascular comorbidities, diabetes mellitus, pulmonary comorbidities, rheumatoid arthritis, and other cancers were registered as comorbidities. Polypharmacy was defined as the use of five or more systemic drugs at the start of immunotherapy. CMS was retrospectively reviewed and data on patient treatment regimen, defined as ICI monotherapy or combination of ICI and chemotherapy, and previous chemotherapy were collected.

2.3. Endpoints and Assessments

Patients were followed from the first administration of any one of the PD-1 and PD-L1 inhibitors within the study period until one month after discontinuation, the end of the study period or death, whichever occurred first. The end of the study period was December 2020.

We manually extracted data on irADRs, medication prescriptions and hospitalisations from the EPFs. Data on adverse events are routinely collected and documented in the EPF by oncologists and oncology nurses during a structured assessment prior to administering each dose of immunotherapy. Adverse events were considered irADRs if they resembled an auto-immune reaction and developed, or exacerbated, after starting treatment with a PD-1 or PD-L1 inhibitor. The included irADRs were based on the guidelines of the European Society for Medical Oncology (ESMO) about management of toxicities from immunotherapy [13].

The severity of the irADRs was categorised as mild (asymptomatic or mild symptoms, no therapy needed), moderate (local or oral medication needed, but no hospitalisation), or severe (hospitalisation needed or life threatening; urgent intervention indicated). Accordingly, additional data was collected from the EPF on possible prescriptions or hospitalizations after the registration of the adverse event. If a patient experienced multiple irADRs, all of these were documented. If a patient experienced the same irADR multiple times, the event with the highest grade was registered. irADRs concerning cutaneous reactions (dermatitis, pruritus, and dry skin) were combined as cutaneous irADRs. irADRs concerning diarrhoea and colitis were combined as non-infectious diarrhoea/colitis.

2.4. Statistical Analysis

The following patient subgroups were made based on the age at the start of (chemo-)immunotherapy: <65 years old and ≥ 65 years old. Statistical heterogeneity of ECOG score, treatment regimen, combination therapy, previous treatment with cytostatic agents, polypharmacy, PD-L1 status, and type of malignancy between the two age groups were analyzed using the Pearsons Chi-square test with a p-value <0.05 indicating a statistically significant difference.

A Pearson's Chi-square test was used to compare irADRs between the two age categories (<65 and ≥ 65). A Fisher's exact test was performed on irADRs with a count less than five in any of the age. In addition, age was also studied as a linear variable in order to obtain more information about the age distribution of irADRs. Subgroup analyses were also performed for each drug type. All analyses were carried out using SPSS, version 24.

3. Results

From September 2016 until September 2019, a total of 217 patients were treated with PD-1 or PD-L1 inhibitors at Haga Teaching hospital and were included in our study. 183 patients (84.3%) were treated with monotherapy with PD-(L)1 inhibitors and 34 (15.7%) with chemo-immunotherapy. Ninety-two patients (42%) were younger than 65 years of age and 125 patients (58%) were 65 years of age or older at the start of immunotherapy. The median age of our patients was 66.0 years. Older patients had significantly more cardiovascular comorbidities. Other baseline demographics, clinical characteristics, and treatment characteristics are comparable between the two groups (Table 1).

A total of 278 irADRs were registered in the study period for all four ICIs. Cutaneous irADRs (53.9%), thyroid gland disorders (20.3%), and non-infectious diarrhoea/colitis (17.5%) were the most frequently reported ADRs. Neuropathy (11.1%), hepatitis (9.2%), and pneumonitis (7.4%) were reported in more than 5% of the patients. Table 2 shows an overview of all irADRs that occurred in our study.

No difference was seen between the two age categories, in the cumulative incidence of most irADRs. The cumulative incidence of reported skin toxicity did however differ between the age groups: skin toxicity was reported in 45.7% of the patients <65 years and in 60.0% of the patients ≥65 years ($p = 0.036$). However, there was a positive, non-significant, association between age and the occurrence of some irADRs such as hepatitis, pneumonitis, and nephritis. Analyzing age as a

Table 1
Demographic and clinical characteristics of the cohort.

		Total $N = 217$	<65 years $N = 92$ (42.4%)	≥65 years $N = 125$ (57.6%)	P-value Chi-square
Age, median (range)		66.0 (28-86)	59 (28-64)	70 (65-86)	n.a.
Sex, N (%)	Female	96 (44.2)	46 (50.0)	50 (40.0)	0.14
BMI, median (IQR)		24.6 (21.8–27.7)	24.1 (21.6–28.1)	24.6 (21.9–27.1)	0.54
ECOG-score, N (%)	0	114 (52.5)	52 (56.5)	62 (49.6)	0.31
	1	79 (36.4)	30 (32.6)	49 (39.2)	0.320
	2	5 (2.3)	1 (1.1)	4 (3.2)	0.31
	3	1 (0.5)	0 (0.0)	1 (0.8)	n.a.
	Unknown	18 (8.3)	9 (9.8)	9 (7.2)	0.50
Treatment regimen, N (%)	Nivolumab	78 (35.9)	33 (35.9)	45 (36.0)	0.98
	Pembrolizumab	92 (42.4)	38 (41.3)	54 (43.2)	0.78
	Atezolizumab	36 (16.6)	18 (19.6)	18 (14.4)	0.31
	Durvalumab	11 (5.1)	3 (3.3)	8 (6.4)	0.30
Malignancy type, N (%)	NSCLC	164 (75.6)	71 (77.2)	93 (74.4)	0.64
	RCC	19 (8.7)	5 (5.4)	14 (11.2)	0.14
	UCC	21 (9.7)	8 (8.7)	13 (10.4)	0.67
	Other	13 (6.0)	8 (8.7)	5 (4.0)	0.15
Chemo-immunotherapy, N (%)	Yes	34 (15.7)	16 (17.4)	18 (14.4)	0.55
Formerly treated with cytostatic therapy, N (%)	Yes	149 (68.7)	65 (70.7)	84 (67.2)	0.59
PD-L1 status, N (%)	Negative (<1%)	38 (17.5)	16 (17.4)	22 (17.6)	0.97
	Positive (1–50%)	19 (8.8)	7 (7.6)	12 (9.6)	0.61
	Strongly positive (>50%)	56 (25.8)	22 (23.9)	34 (27.2)	0.58
	Unknown	104 (47.9)	47 (51.1)	57 (45.6)	0.42
Geriatric data					
Polypharmacy, N (%)	Yes	127 (58.5)	52 (56.5)	75 (60.0)	0.61
Comorbidities, N (%)	Cardiovascular	120 (55.3)	43 (46.7)	77 (61.6)	0.03
	Diabetes Mellitus	39 (18.0)	14 (15.2)	25 (20.0)	0.37
	Pulmonary	65 (30.0)	32 (34.8)	33 (26.4)	0.18
	Rheumatoid arthritis	9 (4.1)	1 (1.1)	8 (6.4)	0.05
	Other cancer	23 (10.6)	7 (7.6)	16 (12.8)	0.22

Acronyms: BMI=Body Mass Index; IQR = Interquartile Range; ECOG = Eastern Cooperative Oncology Group; NSCLC=Non Small Cell Lung Carcinoma; RCC = Renal Cell Carcinoma; UCC=Urethral Cell Carcinoma.

Table 2
Frequency of immune-related adverse drug reactions among younger and older patients.

	Total, $N = 217$	<65 years, $N = 92$	≥65 years, $N = 125$	p-value Chi-square (Fisher's exact)[a]
Cutaneous irADRs, N (%)	117 (53.9)	42 (45.7)	75(60.0)	0.036
Thyroid gland disorders, N (%)	44 (20.3)	20 (21.7)	24 (19.2)	0.646
Non-infectious diarrhoea/colitis, N (%)	38 (17.5)	18 (19.6)	20 (16.0)	0.495
Neuropathy, N (%)	24 (11.1)	12 (13.0)	12 (9.6)	0.424
Hepatitis, N (%)	20 (9.2)	6 (6.5)	14 (11.2)	0.239
Pneumonitis, N (%)	16 (7.4)	6 (6.5)	10 (8.0)	0.680
Rheumatoid arthritis, N (%)	10 (4.6)	5 (5.4)	5 (4.0)	0.618
Nephritis, N (%)	7 (3.2)	2 (2.2)	5 (4.0)	0.701
Pancreatitis, N (%)	2 (0.9)	2 (2.2)	0 (0)	0.179

[a] A chi-square test was used to compare irADRs between the two age categories. Fisher's exact test was performed on irADRs with a count less than 5 in any of the age categories.

continuous variable also demonstrated an increased risk of skin toxicity with increased age.

In subgroup analysis for individual PD-1 inhibitors, the cumulative incidence of cutaneous irADRs was significantly higher in older patients receiving nivolumab ($p = 0.039$). There was no statistically significant association between age and the incidence of cutaneous irADRs in the pembrolizumab group.

Lastly, in subgroup analysis of PD-L1 inhibitors (atezolizumab and durvalumab), the incidence of skin toxicity was found to be not significantly higher in older patients (dichotomous: $p = 0.391$). These findings were also confirmed when age was analyzed as a linear variable.

The majority of the reported irADRs, 253 (91.3%) were mild or moderate reactions. Only 18 (6.5%) of the irADRs were severe and needed hospitalisation. Table 3 shows an overview of all severe ADRs. Non-infectious diarrhoea/colitis (3.2%), pneumonitis (2.3%), and hepatitis (1.8%) were the most frequently reported severe irADRs. Death as a result of irADRs did not occur in our population.

46% of the severe ADRs occurred in patients below the age of 65, while this group made up 42% of the total population. Due to the limited number of reported severe ADRs, no statistical analyses were performed on these data.

Table 4 shows the cumulative incidence and the severity of irADRs per drug. The incidence of the irADRs differed between the different ICIs. There seems to be a higher percentage of mild and moderate irADRs in durvalumab users compared to other PD-(L)1 inhibitors, while severe irADRs did not occur in this group.

Non-infectious diarrhoea/colitis was less often reported in nivolumab users (9.0%) and most often in patients treated with pembrolizumab (20.7%). In our study rheumatoid arthritis was only observed in patients using PD-1 inhibitors (nivolumab 6.4%;

Table 3
Severe immune-related adverse drug reactions that resulted in hospitalisation.

	Total, $N = 217$	<65, $N = 92$	≥65, $N = 125$
Non-infectious diarrhoea/colitis, N (%)	7 (3.2)	4 (4.3)	3 (2.4)
Pneumonitis, N (%)	5 (2.3)	2 (2.2)	3 (2.4)
Hepatitis, N (%)	4 (1.8)	2 (2.2)	2 (1.6)
Cutaneous irADRs, N (%)	1 (0.5)	0 (0.0)	1 (0.8)
Nephritis, N (%)	1 (0.5)	0 (0.0)	1 (0.8)

Table 4
Immune-related adverse drug reactions and severity per PD-1/PD-L1 inhibitor.

	Pembrolizumab (n = 92)		Nivolumab (*n* = 78)		Atezolizumab (*n* = 36)		Durvalumab (*n* = 11)	
	Mild/moderate	Severe	Mild/moderate	Severe	Mild/Moderate	Severe	Mild/moderate	Severe
Cutaneous irADRs, N(%)	48 (52.2)	0 (0.0)	38 (48.7)	1 (1.3)	21 (58.3)	0 (0.0)	9 (81.8)	0 (0.0)
Thyroid gland disorders, N (%)	21 (22.8)	0 (0.0)	14 (17.9)	0 (0.0)	3 (8.3)	0 (0.0)	6 (54.5)	0 (0.0)
Non-infectious diarrhoea/colitis, N (%)	19 (20.7)	3 (3.3)	7 (9.0)	3 (3.8)	4 (11.1)	1 (2.8)	2 (18.8)	0 (0.0)
Neuropathy, N (%)	5 (5.4)	0 (0.0)	13 (16.7)	0 (0.0)	3 (8.3)	(0.0)	3 (27.3)	0 (0.0)
Hepatitis, N (%)	9 (9.8)	1 (1.1)	4 (5.1)	2 (2.6)	3 (8.3)	1 (2.8)	0 (0.0)	0 (0.0)
Pneumonitis, N (%)	3 (3.3)	1 (1.1)	4 (5.1)	0 (0.0)	3 (8.3)	4 (11.1)	1 (9.1)	0 (0.0)
Rheumatoid arthritis, N (%)	5 (5.4)	0 (0.0)	5 (6.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nephritis, N (%)	3 (3.3)	0 (0.0)	1 (1.3)	1 (1.3)	2 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatitis, N (%)	1 (1.1)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

pembrolizumab 5.4%). On the other hand, pneumonitis was more often present in the PD-L1 inhibitors (atezolizumab 8.3% mild/moderate irADR, 11.1% severe irADR; durvalumab 9.1% mild/moderate irADR). As can be seen, thyroid gland disorders appeared in 8.3% of the atezolizumab users whereas over 54% of the durvalumab users experienced this irADR.

4. Discussion and Conclusion

The results of this study suggest that the safety of PD-1 and PD-L1 inhibitors is comparable between older and younger patients. There was however a higher incidence of skin toxicity in older patients. The majority of the reported irADRs were mild or moderate reactions. irADRs leading to death were not seen in our study.

The frequency of most irADRs of ICI users was found to be comparable between patients younger than 65 years and those aged 65 years or above. This is line with findings in other real-world studies [14–17]. Also, a pooled analysis of the KEYNOTE-010, −024, and − 042 trials, concluded that the safety profile of pembrolizumab in patients ≥75 years was comparable to that of the overall population [18]. A prospective observational study with a cohort of NSCLC and melanoma patients has found no significant difference in the incidence of immune-related adverse events (irAEs) grade 3–5 between older and younger patients receiving ICIs (18.6% versus 12.9%; odds ratio 1.55, 95% CI 0.61–3.89;$P = 0.353$) [19]. In a global single-arm safety study of NSCLC patients treated with atezolizumab monotherapy, the treatment related adverse events (AEs) occurred in 53.7% of the overall population vs. 55.3% in patients ≥75 years. The incidence of serious AEs (28.3% vs 25%) and irAEs (9.6% vs 10.5%) was also comparable between younger and older patients. [20]. These findings were also confirmed in a cohort of patients with urinary tract carcinoma who were treated with atezolizumab [21].

In our study, skin toxicity (45.7% vs. 60.0%; $p = 0.036$), occurred more frequently in older patients. When performing subgroup analysis, the age difference of cutaneous irADRs remained significant in the nivolumab group but not in pembrolizumab users. Our findings are in line with other similar studies [22,23]. Pedari et al. also showed a higher incidence of dermatological toxicities in patients older than 70 years treated with ICIs. However, in contrast to our results, a significantly higher incidence of endocrine irAEs was reported in younger patients than in the older group [22]. Aging is associated with significant structural and functional impairments of the skin, which may lead to a higher risk of cutaneous ADRs in frail, older patients.

The most frequently occurring irADRs identified in our study were skin toxicity (53.9%), thyroiditis (20.3%), and non-infectious diarrhoea/colitis (17.5%). This is largely in line with the findings of a recent retrospective observational study by Cavaille et al. in which the safety of pembrolizumab in patients with NSCLC was investigated. Cutaneous toxicities (36.6%), hepatic and gastrointestinal reactions (48.8%) were the most frequently observed irADRs in this study [24]. In contrast to these findings, in another real-world study on the safety of nivolumab in metastatic renal cell carcinoma, ADRs of any grade were reported only in 32% of the subjects. Rash, and diarrhoea were experienced by 9%, and 5% of the patients respectively, other irADRs were reported even less frequently. In this study, irADRs were defined as all the AEs that the investigators classified as potentially related to treatment [25]. The subjective classification of ADRs by individual investigators may explain the inconsistent findings of the different real world data studies. These differences were also studied by Bayraktar-Ekincioglu et al. who concluded that an assessment of side effects by healthcare providers in patients with cancer may be challenging due to an increased workload in clinics and undistinguishable symptoms of side effects and cancer itself [26].

Most of the identified ADRs in our study are also reported as frequently occurring AEs in the Summary of Product Characteristics (SmPC) texts for pembrolizumab monotherapy and also for nivolumab [27,28]. It is important to note that cutaneous toxicity is only mentioned in the SmPC of nivolumab and not in the SmPC of pembrolizumab. Considering that both drugs have the same mechanism of action, the difference in reported cutaneous toxicity seems contradictory. According to the SmPC text, the most common AEs for combination chemo-immunotherapy with pembrolizumab include anaemia, nausea, fatigue, constipation, diarrhoea, neutropenia, decreased appetite, and vomiting [27], which is only partially consistent with our findings. An explanation for this difference could be that the described AEs in the SmPC were also included when causality was low or not reported, while in our study we only registered irADRs when the event was expected to be caused by immunotherapy. We believe that the reported AEs in the SmPC are predominantly caused by chemotherapy and are, strictly speaking, not considered irADRs of immune checkpoint inhibitors. This emphasizes the differences between assessing drug safety in clinical trials and post marketing surveillance and thus the necessity of RWD [29].

Among all the severe reactions, colitis, pneumonitis, and hepatitis had the highest frequency, which is consistent with the findings of the ELDERS study [19].

The results of the severity of irADRs are largely in line with other real-world studies. In an Italian cohort of 371 patients with advanced NSCLC receiving nivolumab, the rate of any-grade ADRs vs. grade 3–4 ADRs was 29% and 6% respectively, which is largely in line with our findings [30]. In a real-world retrospective observational study Cavaille et al. concluded that 90% of the reported ADRs of pembrolizumab were grade 1 or 2. Severe ADRs only occurred in patients with ECOG performance score 2–3 [24]. In contrast to severe irADRs, the occurrence of mild or moderate irADRs does not lead to discontinuation, postponement or dose reduction in clinical practice. Based on these findings, it seems likely that older age is not associated with more severe adverse drug reactions.

An important strength of this study is the use of real-world data, which gives an accurate representation of routine clinical practice. Unlike clinical trials, our study included a considerable number of frail older patients, which allows us to extrapolate our findings to the general

older population with cancer. Due to the routine assessment of all patients prior to each dose of immunotherapy, the risk of underrepresentation of irADRs is quite low in our study. Limitations of the study include, the variation in the registration of the irADRs by different caregivers and the small number of patients in the durvalumab and atezolizumab cohorts. Thirty-four patients (15.7%) received chemo-immunotherapy in this study. One cannot rule out the possibility that the identified irADRs in this group may be, at least partially, attributable to the co-administered chemotherapy agents.

In conclusion, we demonstrated that PD-1 and PD-L1 inhibitors can be safely prescribed independent of age. Except for mild and moderately severe skin toxicity, no significant differences were found between younger and older patients.

Ethics Approval and Consent to Participate

This research was approved by the Board of Directors of Haga Teaching hospital. The local Medical Ethical Review Committee (METC Leiden Den Haag Delft) granted a waiver for obtaining informed consent.

Consent for Publication

We give our consent for the publication of the article 'Real-life safety of PD-1 and PD-L1 inhibitors in older patients with cancer: an observational study at Haga Teaching hospital' in the Journal of Geriatric Oncology.

Availability of Data and Materials

Data used in our study is stored on the network storage of the Haga Teaching Hospital and will be available if necessary.

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Authors' Contributions

Contribution: Name(s) of author(s).

Study concepts: Bert N Storm, Erik B Wilms, Frederiek van den Bos, Loes E Visser.

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Declaration of Competing Interest

None.

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