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ORIGINAL ARTICLE

PARIS score for evaluation of probability of SARS-CoV-2 infection in cancer patients

Candice Gueuning[1] · Lieveke Ameye[2] · Angela Loizidou[1] · Bogdan Grigoriu[1] · Anne-Pascale Meert[1]

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Abstract

Control of transmissible diseases as COVID-19 needs a testing and an isolation strategy. The PARIS score developed by Torjdman et al. was aimed at improving patient selection for testing and quarantining but was derived from a general population. We performed a retrospective analysis of the validity of the PARIS score in a cancer patient population. We included 164 patients counting for 181 visits at the emergency department of the Jules Bordet Institute between March 10th and May 18th which had a SARS-CoV-2 RT-PCR test at admission. Twenty-six cases (14.3%) were tested positive with a higher proportion of positive tests among hematological patients compared to those with solid tumors (26% vs 11% $p=0.02$). No clinical symptoms were associated with a positive SARS-CoV-2 PCR. No association between anticancer treatment and SARS-CoV-2 infection was found. The PARIS score failed to differentiate SARS-CoV-2-positive and SARS-CoV-2-negative groups (AUC 0.61 95% CI 0.48–0.73). The negative predictive value of a low probability PARIS score was 0.89 but this concerned only 11% of the patients. A high probability PARIS score concerned 49% patients but the positive predictive value was 0.18. CT scan had a sensitivity of 0.77, specificity 0.51, a positive predictive value of 0.24, and a negative predictive value of 0.92. The performance of the PARIS score is thus very poor in this cancer population. A low-risk score can be of some utility but this concerns a minority of patients.

Keywords Cancer · SARS-CoV-2 infection · COVID-19 · Risk stratification

Introduction

Among cancer patients, community respiratory viruses are the most common causes of respiratory infections [1] and adverse outcomes occur more frequently in comparison to immunocompetent patients [2]. In various Chinese studies, up to 3% of patients with COVID-19 had cancer, a figure much higher than the 0.29% overall cancer incidence in the same populations [3]. The mortality rate in these patients is also increased [4]. In the hematopoietic cell transplant population, age, lymphopenia, high-dose total body irradiation, and the presence of co-pathogens are significant risk factors for progression of a viral upper respiratory tract infection to a lower respiratory tract infection [5–7]. Previous reports concerning cancer patients and COVID-19 highlighted the following predisposing factors for severe complications such as intensive care unit (ICU) admission and death: Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≥ 2 and progressive oncologic disease, presence of metastases, anti-cancer treatment administrated within 14 days, hematological malignancies, contact with health care providers with COVID-19, and patients with solid tumors [8–12].

Reverse transcription polymerase chain reaction (RT-PCR) is currently the reference test to diagnose patients with SARS-CoV-2 infection [13]. Computed tomography (CT) scan has a reported high sensitivity [14] but intrathoracic radiological signs can be delayed after clinical disease onset, with up to 56% CT negativity in the first 3 days of symptomatic infection [15]. Imaging is indicated in case of moderate to severe disease manifestations, but can be

✉ Anne-Pascale Meert
ap.meert@bordet.be

1 Service de Médecine Interne, Institut Jules Bordet, Université Libre de Bruxelles (ULB), Brussels, Belgium

2 Data Center, Institut Jules Bordet, Université Libre de Bruxelles (ULB), Brussels, Belgium

omitted in case of mild symptoms consistent with COVID-19 and no risk factors for disease progression. Even though CT scans may have a higher sensitivity than PCR (71–95% for PCR and 97–98% for CT), their specificity is lower and radiologists may experience difficulties for differentiating SARS-CoV-2 from non-SARS-CoV-2 pneumonia [16]. Moreover, false-negativity of PCR, a negative CT, and SARS-CoV-2 pneumonia mimickers on CT may lead to inaccurate diagnoses.

In these situations, a Bayesian approach of the diagnosis with the calculation of a pre-test probability combining clinical and biological features has proven to be a very useful tool and is already used in clinical practice in the management of patients with suspected pulmonary embolism [17]. Such an approach could help a better identification of the population at risk which need to be tested and can improve patient management in the pretest and time-to-result periods but can also improve diagnostic confidence in PCR-negative cases.

A new prediction score called "Pre-test probability for SARS-CoV-2 Infection based on Scoring (the "PARIS score")" has been developed by Tordjman et al. [18]. The score (ranged from 0 to 5) is based on the evaluation of complete blood cell count (lymphocytes < 1.3 G/L, eosinophiles < 0.06 G/L, basophiles < 0.04 G/L, and polymorphonuclear < 5 G/L) and has been reported to have a good performance to evaluate the pre-test probability of SARS-CoV-2 infection and to identify groups at low and high risk of infection. This approach could help to avoid or delay diagnostic testing in low-risk patients and quarantining the high-risk patient group until obtaining a negative RT PCR test as well as negative CT scanner. The original publication of Tordjman et al. claimed a negative predictive value (NPV) for a low score/low risk (0–1) of 98% while the positive predictive value (PPV) for a high score/high risk (4–5) was between 80 and 92%. The overall disease prevalence in the studied population was 64% but analysis of different time periods showed a similar discriminant capability down to a disease prevalence of 31%. However, it has to be remembered that NPV and PPV values are strongly affected by the prevalence of the disease in the tested population [18].

To date, a number of other similar approaches have been proposed [19] but the PARIS score is simple to use in clinical practice and is requiring readily available data. However, this score has never been evaluated in cancer patients whose biological parameters used to calculate the score are often altered by the disease and/or the therapy.

The aim of our study is to evaluate if the PARIS score remains useful in cancer patients for evaluating the pre-test probability of SARS-CoV-2 infection.

Patients and methods

We performed a retrospective study by including patients presenting at the emergency department of the Jules Bordet Institute between March 10 and May 18, 2020. All patients irrespective of their tumor type (solid tumor or hematological malignancy) and cancer status (diagnostic period, treatment, or follow-up) were eligible provided they had an unplanned visit at the emergency department whatever the reason and were tested with a SARS-CoV-2 RT-PCR test on a naso-pharyngeal swab.

The following data were extracted from medical records: symptoms, comorbidities, performance status, type and stage of cancer, anti-cancer treatment, blood count, results of thoracic imaging, and outcome.

The evaluation of the CT scans and the quantification of disease extent were performed according to the recommendations of the European society of radiology [20]. A grading of the pulmonary involvement was coded as follows: grade 0, no involvement; grade 1, < 10%; grade 2, 10–25%; grade 3, 25–50%; grade 4, 50–75%; grade 5, > 75%.

The study was approved by our Ethical Committee on 21/09/2020 (n°CE3213).

Statistical analysis

Based on the results of the SARS-CoV-2 PCR test, positive and negative patients groups were compared in terms of symptoms, comorbidities, performance status, type and stage of cancer, anti-cancer treatment, blood count, imaging results, and outcome (vital status at 30 days after emergency department admission). For categorical variables, a likelihood chi-square test, Mantel–Haenszel chi-square test, or Fisher exact test was used while continuous variables were assessed with the Mann–Whitney test. A $p < 0.05$ was considered significant.

We assessed the diagnostic performance of the PARIS score (considering the 3 classes: low-probability, intermediate, and high probability) in terms of sensitivity and specificity. The NPV and PPV were also calculated on the same population with a focus on the NPV in the low probability class. The 95% confidence intervals (CI) for all parameters were calculated using the Wilson method. We calculated the area under the ROC curve with 95% CI.

The sample size calculation performed before starting the study was as follows: statistical assumptions were made for $n = 170$ patients expected to be included and a 15 to 20% prevalence of positive SARS-CoV-2 test: 100 patients in the low probability class, 42 in the intermediate, and 7 in the high probability class. Assuming an undegraded sensitivity of 80% as in the general population

[18]: with $n = 30$ SARS-CoV-2-positive patients, the 95% CI for sensitivity would be 63 to 90%.

For an expected NPV of 99%, in an $n = 100$ population with a low-probability PARIS score, the lower 95% CI limit would be 95%. For a PPV of 92%, assuming $n = 27$ cases with high-probability PARIS score, the 95% CI limits would be 77 to 98%.

Results

A total of 164 patients were admitted in the emergency department (ED) between March 10 and May 18, 2020, and tested with an RT-PCR test on a naso-pharyngeal swab for SARS-CoV-2 RNA presence for a total of 181 tests with 16 patients tested negative twice and one patient tested thrice (Table 1). The median number of days between two presentations was 17 days (min 9 days) with a mean 19.1 ± 7.6 days. We thus considered these as separate events. No previously positive patients were tested twice. Demographic data of recruited patients is presented in Table 2.

Out of the 181 SARS-CoV-2 tests performed: 155 were negative and 26 were positive of which 8 were treated as outpatients, 18 were hospitalized, and 6 of them died while 12 were discharged alive. Out of these, 139 had solid tumors and 42 hematological malignancies (Table 2). The proportion of COVID-19-positive tests was higher in hematological patients: 26% (11/42) vs. 11% (15/139) in solid tumor ($p = 0.02$).

Cough, myalgia, and digestive symptoms were statistically more frequent in SARS-CoV-2-positive patients, 62%, 19%, and 35% respectively compared to 37% ($p = 0.02$), 5% ($p = 0.02$), and 13% ($p = 0.02$) in patients without SARS-CoV-2 infection. There was no statistical association between a PCR SARS- CoV-2-positive result and other symptoms such as headache ($p = 0.21$) or temperature > 37.5 °C during the last 72 h ($p = 0.16$).

Table 1 The PARIS score for evaluation of pre-test probability of SARS-CoV-2 infection

Variable	Number of points
Eosinophils < 0.06 G/L	1
Lymphocytes < 1.3 G/L	2
Neutrophils < 5 G/L	1
Basophils < 0.04 G/L	1

Total score obtained by adding the four individual values: Total score values from 0 to 5

Score 0–1 Low probability

Score 2–3 Intermediate probability

Score ≥ 4 High probability

A total of 75 patients (41%) received an anti-cancer treatment in the last 14 days before PCR testing and 29 (16%) within 14 to 30 days. We found no association between administration of an anti-cancer treatment and a positive swab.

For each biological parameter of the PARIS score, a comparison was made between the SARS-CoV-2-positive and SARS-CoV-2-negative population but only the total neutrophil count differed between positive and negatively tested individuals (median 2965 cells/mm^3 and 4840 cell/mm^3 respectively $p = 0.02$). The other laboratory parameters were not different between PCR SARS-CoV-2-positive and SARS-CoV-2-negative patients (Table 1).

Data available permitted the calculation of a PARIS score for 166 of the 181 visits (Table 3): 18 (11%) were in the low probability risk group (0 and 1), 66 (40%) in the intermediate probability risk group (score 2 and 3), and 82 (49%) in the high probability risk (score 4 and 5). There was no statistical associated between the PARIS score and the SARS-CoV-2 test result ($p = 0.09$). The PARIS score had an area under the ROC curve of only 0.61 (95% CI, 0.48 to 0.73) (Fig. 1). Only 15/24 cases, i.e., 63% of the SARS-CoV-2-positive cases were classified as a "high probability risk" by the PARIS score (95% CI, 43 to 79%). Only 16/142, i.e., 11% (95% CI, 7 to 18%) of the patients with a negative SARS-CoV-2 PCR were classified as "low probability risk"; 53% were in the "low or intermediate probability risk" class: 75/142 (95% CI, 45 to 61%). The predictive value of "low probability risk" score to predict a negative SARS-CoV-2 PCR result was 89% (95% CI, 67 to 97%) ($n = 16/18$); the predictive value of "high probability risk" score to predict a positive SARS-CoV-2 PCR result was 18% (95% CI, 11 to 28%) ($n = 15/82$).

A chest CT scan was performed in 130 out of the 181 presentations. The median grade of pulmonary involvement was 1 in COVID-19-negative patients and 2 in COVID-19-positive patients (Table 4). The chest CT scan was considered suspect for 70 cases of which 53 had a negative RT-PCR test. Out of the 60 negative CT scans, only 5 patients had a positive PCR test. The diagnostic performance of the CT scan was as follows: sensitivity 77% (95% CI, 57 to 90%), specificity 51% (42 to 60%), PPV 24% (16 to 36%), and NPV 92% (82 to 96%).

Discussion

During epidemic episodes, a rapid diagnosis and triage of COVID-19 suspect patients are of paramount importance. This relies mainly on clinical grounds but simple tools like clinical/biological/radiological parameters/scores are of great utility in selecting an appropriate attitude toward acutely ill patients in order to maximize the timely use of

Table 2 Patient characteristics and association with a SARS-CoV-2-positive test result

	All tests ($N=181$)		SARS negative ($N=155$)		SARS positive ($N=26$)		p-value
Age							
Median (IQR)	66 (52 to 73)		65 (51 to 72)		70 (63 to 76)		0.02
Sex							
Female	105	58%	91	59%	14	54%	0.64
Male	76	42%	64	41%	12	46%	
Performance status							
0	45	25%	42	27%	3	12%	0.06
1	68	38%	58	37%	10	38%	
2	33	18%	28	18%	5	19%	
3	25	14%	19	12%	6	23%	
4	10	6%	8	5%	2	8%	
Comorbidities							
Body mass index	($N=135$)		($N=116$)		($N=19$)		
Median (IQR)	24 (21 to 28)		24 (21 to 27)		25 (23 to 30)		0.08
Diabetes							
No	152	84%	133	86%	19	73%	0.14
Yes	32	16%	25	14%	7	27%	
Heart failure							
No	175	97%	150	97%	25	96%	1
Yes	6	3%	5	3%	1	4%	
Stroke (composite of AVC and hemiplegia)							
No	166	92%	145	94%	21	81%	0.05
Yes	15	8%	10	6%	5	19%	
Chronic obstructive pulmonary disease							
No	158	87%	135	87%	23	88%	1
Yes	23	13%	20	13%	3	12%	
Chronic renal failure							
No	181		155		26		
Yes	-		-		-		
Outcome							
Hospitalization							
No	79	44%	71	47%	8	31%	0.14
Yes	99	56%	81	53%	18	69%	
Missing info	3		3		-		
Hospital death (in case of hospitalization)							
No	87	88%	76	94%	11	61%	<0.001
Yes	12	12%	5	6%	7	39%	
Clinical suspicion of SARS-CoV-2 infection							0.77
No	29	16%	26	17%	3	12%	
Yes	152	84%	129	83%	23	88%	
Cancer type							
Hematological	42	23%	31	20%	11	42%	0.02
Solid	139	77%	124	80%	15	58%	
Non-metastatic	58	42%	51	41%	7	47%	0.68
Metastatic	81	58%	73	59%	8	53%	
Hematological:							
Acute myelogenous leukemia	3		2		1		
Acute lymphocytic leukemia	2		2		-		
Myelogenous chronic leukemia	4		3		1		

Table 2 (continued)

	All tests ($N=181$)		SARS negative ($N=155$)		SARS positive ($N=26$)		p-value
Chronic lymphocytic leukemia	2		-		2		
Non-Hodgkin lymphoma	17		11		6		
Hodgkin lymphoma	6		6		-		
Multiple myeloma	3		2		1		
Myelodysplastic syndrome	5		5		-		
Solid:							
Non-metastatic solid:	***58***		**51**		**7**		
Lung	10		9		1		
Gastrointestinal	3		2		1		
Breast	24		24		-		
Urothelial	4		3		1		
Head and neck	8		6		2		
Gynecologic	1		1		-		
Prostate	1		1		-		
Other	9		7		2		
Metastatic solid:	***81***		***73***		***8***		
Lung	19		17		2		
Gastrointestinal	9		9		-		
Breast	20		19		1		
Urothelial	6		5		1		
Head and neck	2		2		-		
Gynecologic	6		4		2		
Prostate	3		1		2		
Other	16		16		-		
Clinical symptoms							
Temperature > 37.5 °C during last 72 h							
No	113	62%	100	65%	13	50%	0.16
Yes	68	38%	55	35%	13	50%	
Rhinorrhea							
No	154	85%	133	86%	21	81%	0.55
Yes	27	15%	22	14%	5	19%	
Cough							
No	108	60%	98	63%	10	38%	0.02
Yes	73	40%	57	37%	16	62%	
Dyspnea							
No	125	69%	106	68%	19	73%	0.82
Yes	56	31%	49	32%	7	27%	
Expectorations							
No	167	92%	144	93%	23	88%	0.43
Yes	14	8%	11	7%	3	12%	
Chest pain							
No	178	98%	152	98%	26	100%	1
Yes	3	2%	3	2%	-	-	
Hemoptysis							
No	180	99%	154	99%	26	100%	1
Yes	1	1%	1	1%	-	-	
Headache							
No	156	86%	136	88%	20	77%	0.21
Yes	25	14%	19	12%	6	23%	

Table 2 (continued)

	All tests (*N* = 181)		SARS negative (*N* = 155)		SARS positive (*N* = 26)		*p*-value
Myalgia							
No	169	93%	148	95%	21	81%	0.02
Yes	12	7%	7	5%	5	19%	
Digestive symptoms							
No	152	84%	135	87%	17	65%	0.02
Yes	29	16%	20	13%	9	35%	
*Biological parameters**	(*N* = 166)		(*N* = 142)		(*N* = 24)		
Neutrophils							
Median (IQR)	4480 (2700–7650)		4840 (2990–8130)		2965 (1785–5530)		0.02
≥ 5G/L	75	45%	69	49%	6	25%	0.03
< 5G/L	91	55%	73	51%	18	75%	
Lymphocytes							
Median (IQR)	845 (480–1230)		835 (520–1230)		850 (415–1120)		0.67
≥ 1.3G/L	38	23%	33	23%	5	21%	1
< 1.3G/L	128	77%	109	77%	19	79%	
Eosinophils							
Median (IQR)	0.03 (0–0.10)		0.03 (0–0.10)		0.01 (0–0.05)		0.06
≥ 0.06G/L	57	34%	52	37%	5	21%	0.17
< 0.06G/L	109	66%	90	63%	19	79%	
Basophils							
Median (IQR)	0.03 (0.01–0.05)		0.03 (0.01–0.05)		0.02 (0.01–0.05)		0.43
≥ 0.04G/L	67	40%	59	42%	8	33%	0.51
< 0.04G/L	99	60%	83	58%	16	67%	

*For each biological parameter, the 1st *p*-value is testing difference in the continuous variable, the 2nd *p*-value is testing difference in the binary variable. IQR = Q1 to Q3 (1st quartile to 3rd quartile of the variable's distribution)

Table 3 Validation of the PARIS score

	All tests (*N* = 181)		SARS negative (*N* = 155)		SARS positive (*N* = 26)		*p*-value
PARIS score							0.09
0	9	5%	9	6%	-	-	
1	9	5%	7	5%	2	8%	
2	28	17%	25	18%	3	13%	
3	38	23%	34	24%	4	17%	
4	36	22%	32	23%	4	17%	
5	46	28%	35	25%	11	46%	
Missing data	15		13		2		
Low probability (score 0–1)	18	11%	16	11%	2	8%	
Intermediate probability (score 2–3)	66	40%	59	42%	7	29%	
High probability (score 4–5)	82	49%	67	47%	15	63%	

the more complex diagnostic methods. The PARIS score was proposed as having excellent operational characteristics in the general population, is very simple to use, and can be calculated in any emergency department in less than 1 h. Thus, it was alleged that patients can be correctly managed while waiting the results of molecular testing.

In our retrospective analysis, these findings were not confirmed and thus the PARIS score is probably not applicable to an oncological population.

When comparing our population with the originally published series, the prevalence of positive cases is much lower (14.4%) compared with an average of 68% and a minimum

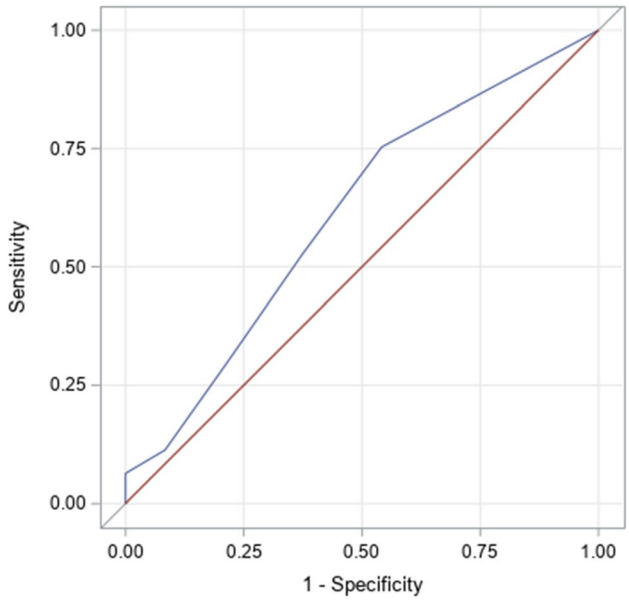

Fig. 1 Area under the ROC curve: 0.61 (95% CI, 0.48 to 0.73)

of 31% in the publication of Tordjman [18]. However, our figures are in line with the disease prevalence in Belgium in the Brussels area during the same period (March 10–May 18, 2020) which was between 9 and 10% for most of the period except during May 2020 when it slowly decreased to around 5% [21]. Oncologic patients are very frequently immunosuppressed and despite taking a lot of precautions, they frequently cannot afford to delay hospital visits (and thus transportation and minimal social contact) which probably explain the higher incidence of positive tests. This prevalence of diseased patients better approaches the real situation in an emergency department than in the population Torjdman studied. The higher prevalence of the disease in the Tordjman series is probably explained by the inclusion of patients hospitalized in a ward.

Among oncological patients, we found that a hematological cancer is a risk factor for having a positive PCR test for SARS-CoV-2 and is very probably explained by the intrinsic state of more profound immunosuppression as well as the treatments received which are often more aggressive. In our population, few symptoms were statistically associated with the diagnosis of SARS-CoV-COVID-19 pneumonia, probably because these symptoms can be explained by primary or metastatic neoplasm, paraneoplastic conditions, or can be related to the treatment of the oncological condition.

One can postulate that the hematological toxicity secondary to the high proportion of patients receiving a chemotherapy prior to emergency department admission is associated with changes in hematological parameters involved in the calculation of the PARIS score and thus explain the difference of our results with those in Tordjman's study in the general population. However, in our analysis, neither treatment received nor time from treatment to ED admission was associated with an increased risk of a positive PCR. Thus, the use of an immunosuppressive treatment alone cannot explain the lack of validity of the PARIS score. It would therefore be interesting to study the PARIS score in samples from a non-oncological population but benefiting from immunosuppressive therapy as for example the organ transplant population.

We performed a simulation of the positive predictive values at different levels of disease prevalence (not presented

Table 4 Analysis of chest CT scan results

	All ($N=181$)		No COVID-19 ($N=155$)		COVID-19 ($N=26$)		*p*-value
Chest CT scan performed							
No	51	28%	47	30%	4	15%	0.16
Yes	130	72%	108	70%	22	85%	
Grading of pulmonary involvement [1]							
0	47	36%	43	40%	4	18%	
1	40	31%	34	32%	6	27%	
2	24	19%	18	17%	6	27%	
3	12	9%	10	9%	2	9%	
4	5	4%	2	2%	3	14%	
5	1	<1%	-	-	1	5%	
Missing data	1		1		-		
Median (Q1–Q3)			1		2		0.008
Suspect CT scan							
No	60	46%	55	51%	5	23%	0.02
Yes	70	54%	53	49%	17	77%	

here) that shows that a high PARIS score will be no more useful at higher disease prevalence levels in an oncological population.

The negative predictive value of the PARIS score calculated from our sample was 0.91, which could be very interesting in excluding COVID-19, but at a low disease prevalence rate, this concerns a minority of patients.

Another issue could be an initial overestimation of the validity of the PARIS Score as the population used both for score derivation and score validation had a very high disease prevalence biasing toward a more favorable operational characteristics by blunting the number of false positive. Moreover, the initial score included patients from medicals wards with a possible bias toward more severe COVID-19 cases.

When analyzing each component of the PARIS score individually, only neutropenia was associated with an increased risk of a SARS-CoV-2-positive PCR in our group. However, the median neutrophil count in the negative SARS-CoV-2 PCR population is 4840/mm^3 and is below the threshold associated with an increased risk of positive PCR as defined by the PARIS score ($< 5000/mm^3$). Thus, it is probable that a specific threshold needs to be determined for oncological patients under therapy. Our series was not large enough to permit that kind of analysis.

Interestingly, in our sample, a suspicious chest CT scan was not associated with an increased risk of having a positive SARS-CoV-2 PCR and the sensitivity and specificity were low. This is probably also explained by the fact that the ground glass opacities found in COVID-19 are also found in a number of infections frequently encountered in oncological patients (such as viral pneumonia, pulmonary aspergillosis; carcinomatous lymphangitis and toxicities of anti-cancer treatments). One can postulate that combining CT with the PARIS score may be eventually useful but given the suboptimal operational characteristics of both tests in the oncologic population, this is unlikely to be true.

A number of other similar approaches have been promoted and a recent systematic review has been published [19]. However, data availability precluded us to make a complete comparison between the different scores in our population. It is however probable that similar studies in the oncologic population need to be considered for each of these approaches before they can be promoted in clinical practice.

In conclusion, we showed that the PARIS score has little applicability in an oncological population. Specific score/approaches should be derived for this population.

Author contribution Ameye Lieveke, Loizidou Angela, Grigoriu Bogdan, and Meert Anne-Pascale contributed to the study conception and design. Data collection and analysis were conducted by Ameye L, C Gueuning, A Loizidou, and AP Meert. All authors contributed to the interpretation of the findings. The first draft of the manuscript was written by C Gueuning, B Grigoriu, and AP Meert. L Ameye and A Loizidou provided supervisory support and reviewed this paper. All authors contributed to the revision of the manuscript and approved the final manuscript.

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Data availability On demand

Code availability Not applicable

Declarations

Ethics approval This study was approved by the ethic committee of the Institut Jules Bordet (21/09/2020).

Consent to participate Not applicable

Consent for publication Not applicable

Conflict of interest The authors declare no competing interests.

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