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Review

FDG PET/CT versus Bone Marrow Biopsy for Diagnosis of Bone Marrow Involvement in Non-Hodgkin Lymphoma: A Systematic Review

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Abstract: The management of non-Hodgkin lymphoma (NHL) patients requires the identification of bone marrow involvement (BMI) using a bone marrow biopsy (BMB), as recommended by international guidelines. Multiple studies have shown that [^{18}F]FDG positron emission tomography, combined with computed tomography (PET/CT), may provide important information and may detect BMI, but there is still an ongoing debate as to whether it is sensitive enough for NHL patients in order to replace or be used as a complimentary method to BMB. The objective of this article is to systematically review published studies on the performance of [^{18}F]FDG PET/CT in detecting BMI compared to the BMB for NHL patients. A population, intervention, comparison, and outcome (PICO) search in PubMed and Scopus databases (until 1 November 2021) was performed. A total of 41 studies, comprising 6147 NHL patients, were found to be eligible and were included in the analysis conducted in this systematic review. The sensitivity and specificity for identifying BMI in NHL patients were 73% and 90% for [^{18}F]FDG PET/CT and 56% and 100% for BMB. For aggressive NHL, the sensitivity and specificity to assess the BMI for the [^{18}F]FDG PET/CT was 77% and 94%, while for the BMB it was 58% and 100%. However, sensitivity and specificity to assess the BMI for indolent NHL for the [^{18}F]FDG PET/CT was 59% and 85%, while for the BMB it was superior, and equal to 94% and 100%. With regard to NHL, a [^{18}F]FDG PET/CT scan can only replace BMB if it is found to be positive and if patients can be categorized as having advanced staged NHL with high certainty. [^{18}F]FDG PET/CT might recover tumors missed by BMB, and is recommended for use as a complimentary method, even in indolent histologic subtypes of NHL.

Keywords: positron emission tomography; biopsy; non-Hodgkin lymphoma; bone marrow involvement

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1. Introduction

Non-Hodgkin lymphoma (NHL) is the most common hematological malignancy and is one of the most commonly occurring cancers, accounting for 4% of cancers globally, and is responsible for around 6% of cancer-related mortality [1]. Although incidence rates have increased over time [2], survival rates have improved markedly [3]. In the pediatric population, NHL is considered the fourth most common malignancy and is characterized by a high propensity to bone marrow involvement (BMI) [4]. NHL consists of more than 60 heterogeneous subtypes derived from lymphoid tissues with several biological features. The most common indolent subtype of NHL is follicular lymphoma (FL), which accounts for around 35% of all NHL cases, whereas the most common aggressive subtype of NHL is diffuse large B-cell lymphoma (DLBCL), accounting for 30–40% of all cases [5]. Peripheral

T-cell lymphoma (PTCL) accounts for about 6% of NHLs and mantle cell lymphoma (MCL), which is considered a rare B-cell lymphoma, accounts for around 6% of NHL cases [3]. Other rare subtypes, such as primary mediastinal large B-cell lymphoma (PMBCL) and Burkitt lymphoma (BL) account for approximately 2% of the cases.

In NHL, the accurate detection of the BMI is crucial, as its presence indicates advanced stages and affects the prognosis, clinical management and treatment process [6]. Regarding the Ann Arbor staging system, BMI leads to the transition of the lymphoma to stage IV, as a result of which a more aggressive treatment is required [7]. BMI has also been found to be an indicator of the occurrence of an infusion-related reaction following rituximab administration in patients with B cell non-Hodgkin lymphoma and special care should be taken with regard to patients who have BMI during rituximab treatment [8]. The reference standard method for assessing BMI in NHL patients is the bone marrow biopsy (BMB) in the unilateral or bilateral iliac crest [9]. BMB only investigates a limited section of the bone marrow in the iliac crest, but it has nevertheless been routinely used for many decades as the standard method. This remains the case despite several studies concluding that due to its small sample size and sample error, BMB may have low sensitivity and may miss patchy or focal bone marrow lymphoma outside the iliac crest area. Additionally, complications might occur during BMB, as it is an invasive procedure and can cause bleeding and infection, although the risk is small but nevertheless it is not negligible. Finally, BMB logistics (i.e., decalcification) proves to be time consuming and the waiting period to receive a result may cause treatment delay.

Imaging with [^{18}F]Fluoro-2-deoxy-D-glucose ([^{18}F]FDG) positron emission tomography (PET), combined with computed tomography (CT) (PET/CT), has revolutionized the staging of lymphoma patients. PET/CT is a non-invasive technique that has been established as an important tool for staging of FDG-avid lymphomas such as Hodgkin lymphoma and DLBCL [10]. Several studies have shown that PET/CT may be used as complementary to, or may even replace, BMB, as it provides information from the entire bone marrow compared to BMB, which is limited to the iliac crest area, thus avoiding sampling errors [11,12]. Most of the NHL histopathologic subtypes have shown the presence of high [^{18}F]FDG avidity [13], which justifies the investigation of the usefulness of [^{18}F]FDG PET/CT for the management of NHL patients. Whilst [^{18}F]FDG PET/CT produces non-invasive visualizations of the whole bone marrow, it lacks histological information and not all the FDG avid lesions are lymphomas.

A previous systematic review, conducted in 2005, and meta-analysis by Pakos et al. [14] showed that [^{18}F]FDG PET has low sensitivity for the detection of BMI in NHL patients (i.e., sensitivity and specificity equal to 43% and 88%, respectively). The authors attributed the low sensitivity to the use of studies that included a mixed population of FDG high- and low-avidity NHL histologic subtypes. However, a limitation of this investigation was that all the included studies used PET systems that are diagnostically inferior to current PET/CT systems that have CT-based attenuation correction. In a single PET system, it is also more difficult to localize anatomically small lesions compared to PET/CT. Therefore, a new systematic review is required to analyze PET/CT data. In 2014, Adams et al. [11] focused only on one and the most common aggressive subtype of NHL, the DLBCL, and showed that [^{18}F]FDG PET/CT has 88.7% pooled sensitivity and 99.8% pooled specificity for detecting BMI. In a meta-analysis conducted by Chen et al. [12] in 2011, a separate population for aggressive and indolent NHL patients reported a pooled sensitivity and specificity equal to 74% and 84%, respectively for the detection of BMI in aggressive NHL and 46% and 93%, respectively for indolent NHL. However, two drawbacks were found in the study by Chen et al. [12], namely, that the included studies used either a single PET unit or a PET/CT, and they did not use a standard reference as no biopsy results were available in most of the studies and they were forced to instead rely on other diagnostic procedures that affect the interpretation of the results. The value of [^{18}F]FDG PET/CT in diagnosing BMI in patients with NHL is still a timely question, and remains a subject of debate in the literature.

The purpose of this study was to systematically review published data on the value of [^{18}F]FDG PET/CT in diagnosis of BMI for NHL patients compared to BMB.

2. Materials and Methods

A systematic review was conducted according to the PICO search strategy to answer the review question that included the following elements: Population (Adult and Pediatric NHL patients); Intervention ([^{18}F]FDG PET/CT); Comparison (Bone marrow biopsy); Outcomes (Diagnosis of bone marrow involvement).

2.1. Search Strategy

A search of the databases PubMed and Scopus was conducted to identify the published studies on the value of [^{18}F]FDG PET/CT in diagnosing BMI for NHL patients compared to BMB. The search strategy is illustrated in Table 1.

Table 1. Search strategy and results as on 1 November 2021.

No.	Search Term	Database Search Results	
		PubMed	Scopus
#1	non-Hodgkin OR non-Hodgkins OR PTCL OR Peripheral T-cell lymphoma OR MCL OR mantle cell lymphoma OR DLBCL OR diffuse large B-cell lymphoma OR FL OR Follicular lymphoma OR PMBCL OR Primary mediastinal large B-cell lymphoma OR BL OR Burkitt lymphoma	101,834	193,114
#2	2-fluoro-2-deoxy-D-glucose OR FDG OR Fluorodeoxyglucose OR PET/CT	57,777	91,069
#3	biopsy	323,619	840,810
#4	Bone marrow	229,682	412,081
#5	#1 AND #2 AND #3 AND #4	[Title/Abstract] 155	[Title/Abstract/Keyword] 515

(#) Number of search term.

2.2. Study Selection

2.2.1. Inclusion Criteria

- Studies that analyse [^{18}F]FDG PET/CT's role in diagnosing BMI in comparison to the invasive BMB for NHL patients.
- Studies carried out for NHL patients.
- Studies published in English.
- Studies published until 1 November 2021.

2.2.2. Exclusion Criteria

- Studies that did not involve comparison between the [^{18}F]FDG-PET/CT and BMB.
- Studies that contain only BMB test, or only [^{18}F]FDG-PET/CT exam.
- Studies carried out only for Hodgkin lymphoma patients.
- Studies that include previously diagnosed patients with NHL.
- Studies that did not assess the BMI.
- Studies that did not differentiate between the previously treated patients and HL patients from NHL-diagnosed patients.
- Studies published only as abstracts.
- Case reports, review articles, recommendations, letters, conference abstracts.
- Studies conducted on animals.

The articles were reviewed by applying the inclusion and exclusion criteria used for this study. Any duplicate studies were rejected, and the remaining studies were reviewed to define their eligibility for inclusion in this review.

2.3. Study Quality

The quality of the studies was assessed using the QUADAS-2 tool for the following four domains: patient selection (NHL), index test ([^{18}F]FDG PET/CT), standard reference (BMB), and flow and timing. Each of these domains was applied with consideration of the risk of bias, and the assessment of the first three domains were applied in terms of applicability. Signaling questions were used to help judge the risk of bias. The low risk of bias (L) was recorded in case all the domain questions were judged as "yes"; the potential high risk of bias (H) was considered if one of the questions was judged as "no", and the unclear bias (UN) was recorded in case there was inadequate information to answer the required questions.

2.4. Data Extraction

Data extraction was performed independently by two reviewers. Primary characteristics of the studies included authors name, year of publication, location of study publication, and study design (i.e., retrospective or prospective)]. The participant details were also extracted and summarized (gender, mean age, median age, age range, patient recruitment, number of NHL patients). In addition, data were extracted with regard to the interval time between the PET/CT and BMB, BMB site, image interpretation method, reference standard test, if a PET/CT was performed before or after treatment, and the stage of the disease based on the Ann Arbor staging system [I, II, III, IV]. Finally, the diagnostic performance data (i.e., sensitivity, specificity, positive and negative predictive values) for PET/CT and BMB were also extracted from each study is recorded.

3. Results

3.1. Search Results

The search yielded 670 articles. PubMed: 155 articles; Scopus: 515. Following the removal of duplicate studies, 527 articles remained. These were subjected to screening of their titles and abstracts to examine their eligibility based on the inclusion and exclusion criteria, and 375 articles were discarded. The full text of 152 articles was then reviewed. Of these articles, 111 articles were excluded as they did not follow the inclusion and exclusion criteria described in the flow diagram in Figure 1. The remaining 41 articles were eligible for inclusion in this systematic review. From the eligible studies included in this systematic review, the total sample size comprised 6147 NHL patients.

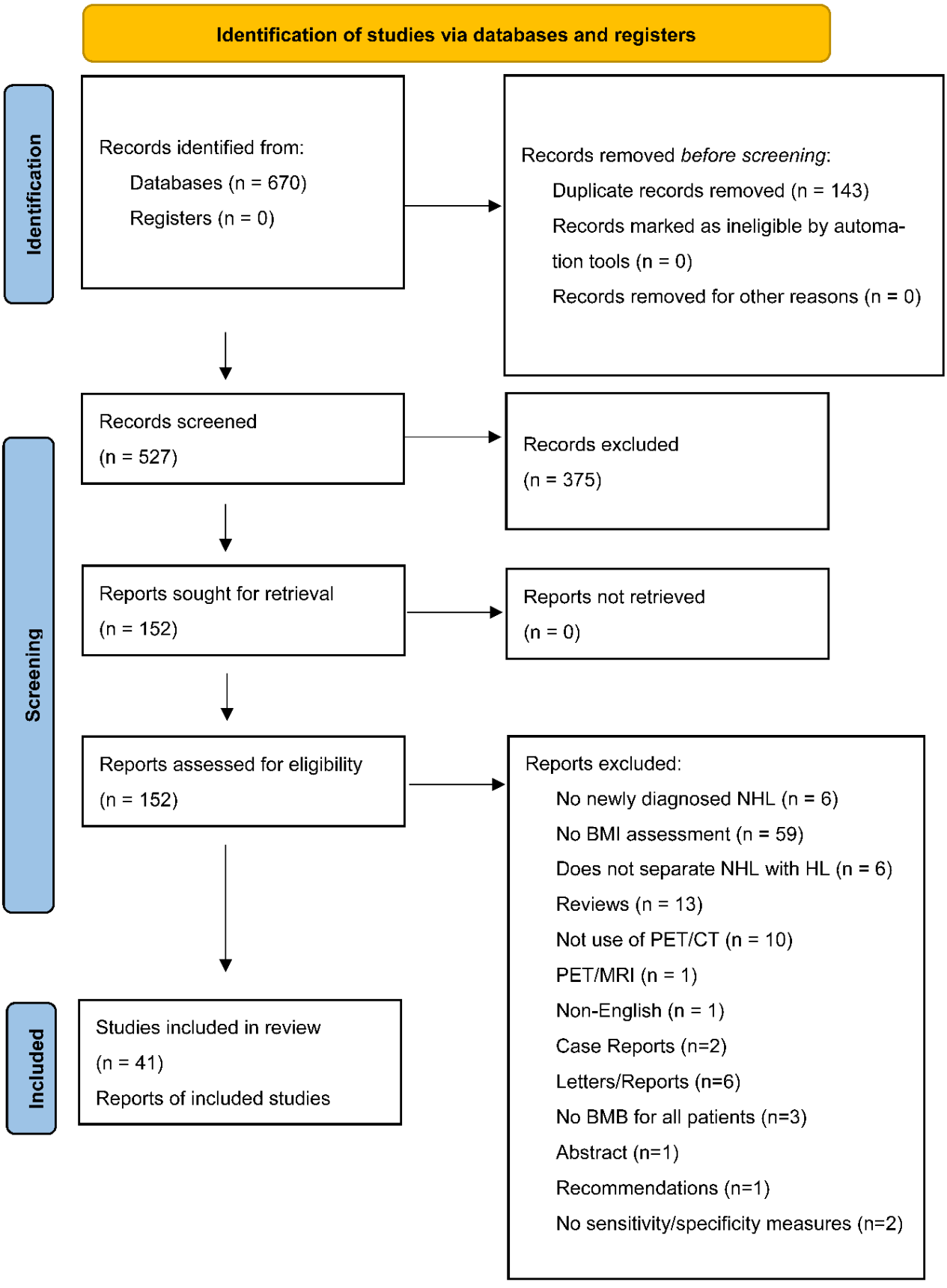

Figure 1. Flow diagram of the search process.

3.2. Characteristics of the Included Studies

This systematic review included 41 studies; 37 studies had a retrospective nature, 2 studies did not mention their nature, while only two studies had a prospective nature. The studies were published from across the world (9 Turkey, 4 China, 4 United States of America, 3 Egypt, 2 Italy, 3 Netherlands, 2 Spain, 2 United Kingdom, 1 Denmark, 1 France, 1 Germany, 1 Hong Kong, 1 India, 1 Japan, 2 South Korea, 1 Lebanon, 1 Malaysian, 1 Mexico, 1 Qatar).

The 41 studies included a total of 6147 NHL patients. Considering the age range, 35 studies included adult patients, 5 studies included paediatric patients and 1 study included a mixed population of adult and paediatric patients.

The [^{18}F]FDG PET/CT and BMB were performed for all patients in the included studies, before treatment in 30 studies, and five studies reported that it was performed before and after treatment, and six studies did not report when it was performed. Among the 41 included studies, 23 articles used the BMB as the reference standard test, 9 articles used both BMB and follow-up [^{18}F]FDG PET/CT, and 9 articles did not mention what they used. Regarding the BMB site evaluation, 24 studies mentioned that it was unilaterally performed at the posterior iliac crest, 5 studies stated that it was performed bilaterally, while the remaining studies did not report any details about this. The interval time between the PET/CT and BMB varied for each study, depending on the NHL subtype from 0 to 0–104 days (Table 2). The interpretation of PET/CT was performed qualitatively in 23 studies and both qualitative and quantitively by using SUV threshold in the remaining 18 studies. Diagnostic performance (sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV)) were recorded for all studies for both PET/CT and BMB.

Table 2. Characteristics of the included studies.

Participants Details							PET/CT before or after	Interval between BMB & PET/CT	BMB Site	PET/CT Interpretation	Standard Reference Test	Ann Arbor Staging Patients No.			
First Author, Publication Year	Country	Pts	No. of Male & Female	Age (Years)	Age Range (Years)	Patient Recruitment						I	II	III	IV
Aguado-Vázquez et al., 2021 [15]	Mexico	297	M 166 F 131	57 Median	Adult 43–66	2017–2018	BT	NR	Unilateral	Qualit.	BMB	31	51	46	169
Kaddu-Mulindwa * et al., 2021 [16]	Germany	930	M 525 F 405	68 Median	Adult 18–80	NR	NR	NR	NR	Qualit.	BMB	NR	NR	501	
Göçer et al., 2021 [17]	Turkey	231	M 138 F 93	FL 60 DLBCL 58 Other 63.5 Median	Adult FL (32–85) DLBCL (18–86) Other (20–85)	2010–2018	BT	<15 days	Unilateral	Qualit.	BMB	FL 3 DLBCL 5 Other 2	FL 5 DLBCL 42 Other 4	FL 15 DLBCL 51 Other 10	FL 23 DLBCL 29 Other 42
Maisarah et al., 2021 [18]	Malaysian	21	M 13 F 8	45.6 Mean	Adult 18–80	2016–2018	BT	<60 days	NR	Qualit./ Quant.	BMB	2	6	5	8
Lim et al., 2021 [19]	South Korea	512	M 283 F 229	57 Median	Adult 47–67	2009–2014	BT	<7 days	Bilateral	Qualit.	BMB	285		83	144
Nakajima et al., 2020 [20]	USA	261	M 135 F 126	58.1 Median	Adult 19.7–90.5	2002–2016	BT	NR	NR	Qualit.	BMB	70	24	47	120
St-Pierre et al., 2020 [21]	USA	548	M 286 F 262	61 Median	Adult 19–91	2003–2016	BT	NR	NR	Qualit./ Quant.	BMB	NR	NR	NR	NR
Al-Sabbagh et al., 2020 [22]	Qatar	89	M 64 F 25	48.6 Mean 48 Median	Adult 18–77	2003–2017	BT	<30 days	Unilateral	Qualit.	BMB	23	12	9	45
Kandeel et al. 2020 [23]	Egypt	88	NR	NR	Adult	2015–2018	BT	<30 days	Unilateral	Qualit./ Quant.	BMB	NR	NR	NR	NR
Kupik et al., 2020 [24]	Turkey	89	M 55 F 34	54 Mean	Adult NR	2011–2013	BT	NR	NR	Qualit./ Quant.	BMB/Follow-up	NR	NR	NR	NR
Elamir * et al., 2020 [25]	Egypt	57	NR	NR	Adult NR	NR	BT	2 weeks	NR	Qualit./ Quant.	BMB/Follow- up	NR	NR	NR	NR
Büyükşimşek et al., 2020 [26]	Turkey	269	M 159 F 110	52 Median	Adult 18–80	2011–2018	BT	2 weeks	Unilateral	Qualit.	NR	45	58	101	65
Tezol et al., 2020 [27]	Turkey	20	M 13 F 7	10.6 Mean	Pediatr. NR	2008–2018	BT	NR	Bilateral	Qualit./ Quant.	BMB	NR	NR	NR	NR
Yang et al., 2020 [28]	China	39	M 30 F 9	58.5 Mean	Adult 42–81	2007–2018	BT/AT	NR	NR	Qualit./ Quant.	BMB/Follow-up	0	3	1	35
Xiao Xue et al., 2020 [29]	China	55	NR	NR	Adult. NR	2016–2017	BT	2 weeks	Unilateral	Qualit.	BMB	NR	NR	NR	NR
Yağci-Küpeli et al., 2019 [30]	Turkey	36	M 26 F 10	7 Median	Pediatr. 2–17	2014–2017	BT	NR	NR	Qualit./ Quant.	NR	NR	NR	NR	NR
Chen et al., 2019 [31]	China	46	M 36 F 10	7 Median	Pediatr. 2–18	2010–2017	BT	NR	Unilateral	Qualit.	BMB/Follow-up	NR	NR	NR	NR

Table 2. *Cont.*

Participants Details							PET/CT before or after	Interval between BMB & PET/CT	BMB Site	PET/CT Interpretation	Standard Reference Test	Ann Arbor Staging Patients No.			
First Author, Publication Year	Country	Pts	No. of Male & Female	Age (Years)	Age Range (Years)	Patient Recruitment						I	II	III	IV
Abe et al., 2019 [32]	Japan	83	M 51 F 32	73 Median	Adult 63.5–78	2006–2018	BT	NR	Unilateral	Qualit./ Quant.	BMB/Follow-up	NR	NR	70	
Badr et al., 2018 [33]	Egypt	27	M 20 F 7	7 Median	Pediatr. 2–16	2010–2015	BT	2 weeks	NR	Qualit./ Quant.	NR	0	9	4	14
Özpolat et al., 2018 [34]	Turkey	22	M 10 F 12	55 Mean	Adult NR	NR	BT	NR	Unilateral	Qualit.	BMB	2	5	5	10
Chen et al., 2018 [35]	China	93	M 66 F 27	8 Median	Pediatr. 1–21	2010–2017	BT	2 weeks	Unilateral	Qualit.	BMB/Follow-up	8	11	51	23
Öner et al., 2017 [36]	Turkey	108	NR	45.3 Mean	Adult & Pediatr. 3–85	2009–2013	BT/AT	10 days	Unilateral	Qualit.	BMB	NR	NR	NR	NR
Teagle et al., 2017 [37]	UK	36	DLBCL M 16 F 8 FL M 4 F 8	DLBCL 58/ FL 59 Median	Adult DLBCL 20–79 FL 33–71	2008–2013	BT	DLBCL (0–104) FL (1–19) days	Unilateral	Qualit.	BMB	DLBCL 4 FL 2	DLBCL 7 FL 2	DLBCL 7 FL 5	DLBCL 6 FL 3
Albano et al., 2017 [38]	Italy	57	M 31 F 26	54.2 Mean	Adult 21–86	2013–2015	NR	10 days	NR	Qualit.	BMB	1	13	9	34
Pham et al., 2017 [39]	USA	16	M 11 F 5	63 Median	Adult 34–72	2001–2015	BT/AT	30 days	NR	Qualit.	NR	NR	NR	NR	NR
El Karak et al., 2017 [40]	Lebanon	54	M 25 F 29	50 Mean	Adult 16–87	2009–2013	BT	NR	NR	Qualit./ Quant.	BMB	10	12	10	22
Yilmaz et al., 2017 [41]	Turkey	201	M 113 F 88	59 Median	Adult 21–87	2007–2013	NR	<7 days	Unilateral	Qualit./ Quant.	NR	NR	NR	NR	NR
Vishnu et al., 2017 [42]	USA	99	M 57 F 42	62 Median	Adult 24–88	2004–2013	BT	<2 weeks	Unilateral	Qualit.	BMB	NR	NR	NR	NR
Alzahrani et al., 2016 [43]	Denmark	530	M 294 F 267	65 Median	Adult 16–90	2007–2013	BT	NR	Unilateral	Qualit.	BMB	197		333	
Chen-Liang et al., 2015 [44]	Spain	232	M 120 F 112	58 Median	Adult 18–85	2009–2014	BT	30 days	Unilateral	Qualit./ Quant.	NR	23	34	69	106
Kim et al., 2015 [45]	South Korea	86	NR	NR	Adult NR	2004–2009	NR	NR	Unilateral	Qualit./ Quant.	BMB	NR	NR	NR	NR
Lee et al., 2015 [46]	Hong Kong	46	M 23 F 23	59 Mean	Adult	2007–2014	BT	4 ± 9 days	Bilateral	Qualit./ Quant.	BMB/Follow-up	NR	NR	NR	NR
Adams et al., 2015 [47]	Netherlands	40	M 24 F 16	66 Mean	Adult 28–88	2007–2013	BT	0–15 days	Unilateral	Qualit.	BMB	NR	NR	NR	NR
Çetin et al., 2015 [48]	Turkey	100	M 59 F 41	NR	Adult 18–85	2008–2012	NR	NR	Unilateral	Qualit.	BMB	1	42	28	29

Table 2. *Cont.*

Participants Details							PET/CT before or after	Interval between BMB & PET/CT	BMB Site	PET/CT Interpretation	Standard Reference Test	Ann Arbor Staging Patients No.			
First Author, Publication Year	Country	Pts	No. of Male & Female	Age (Years)	Age Range (Years)	Patient Recruitment						I	II	III	IV
Cortés-Romera ** et al., 2014 [49]	Spain	84	M 43 F 41	62.5 Median	Adult 19–78	2004–2010	BT	2 weeks	Unilateral	Qualit./ Quant.	BMB	14	28	13	29
Adams et al., 2014b [50]	Netherlands	78	M 42 F 36	69 Median	Adult 33–88	2007–2013	BT/AT	0–26 days	Unilateral	Qualit.	BMB	NR	NR	60	
Adams et al. 2014c [51]	Netherlands	22	M 10 F 12	63.2 Mean	Adult 43–86	2007–2013	BT	<30 days	Unilateral	Qualit./ Quant.	BMB	NR	NR	NR	NR
Berthet et al., 2013 [52]	France	133	NR	57 Mean	Adult 18–87	2006–2011	BT	<60 days	Unilateral	Qualit.	BMB/Follow-up	NR	NR	NR	NR
Khan et al., 2013 [53]	UK	130	M 77 F 53	59 Median	Adult 22–87	2005–2012	BT	1 month	Unilateral	Qualit.	BMB/Follow-up	30	29	26	45
Pelosi ** et al., 2011 [54]	Italy	207	NR	NR	Adult NR	2004–2009	BT/AT	2 weeks	Bilateral	Qualit.	NR	1	10	14	10
Mittal et al., 2011 [55]	India	77	NR	NR	Adult NR	2009–2010	NR	7–10 days	Bilateral	Qualit./ Quant.	NR	NR	NR	NR	NR

Pts = patients, NR = Not Recorded, BT = Before Treatment, AT = After Treatment, Qualit = Qualitative, Quant = Quantitative. All the studies were Retrospective except from * two Prospective studies and ** two studies that did not mention their design.

NHL was classified based on the Ann Arbor staging system in 23 studies, while the remaining studies did not report staging or used a different method. Finally, the subtype of NHL was recorded whenever possible. Among the 41 studies, the total number of patients with diffuse large B-cell lymphoma (DLBCL) was 2336, 1059 for follicular lymphoma (FL), 97 for Mantle Cell lymphoma (MCL), 21 for Burkitt lymphoma (BL), 13 for Primary mediastinal large B-cell lymphoma (PMBCL), and for Peripheral T-cell lymphoma (PTCL) it was 83. In some studies, there was no information regarding the subtype of the NHL, but they generally categorized the patients as having either indolent NHL, aggressive NHL or simply NHL. All the extracted data from the studies are presented in Tables 2 and 3.

Table 3. Summary of the statistical measurements of the included studies. NR = Not Recorded, positive predictive value (PPV), negative predictive value (NPV), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), Burkitt lymphoma (BL), mantle cell lymphoma (MCL), peripheral T-cell lymphoma (PTCL), Primary mediastinal large B-cell lymphoma (PMBCL).

Reference			Sensitivity		Specificity		PPV		NPV	
	NHL Subtype		BMB	PET/CT	BMB	PET/CT	BMB	PET/CT	BMB	PET/CT
Aguado-Vázquez et al., 2021 [15]	DLBCL	n = 154	NR	63.20%	NR	80.00%	NR	30.80%	NR	93.90%
	FL	n = 47	NR	78.60%	NR	78.80%	NR	61.10%	NR	89.70%
	NHL	n = 96	NR	73.30%	NR	85.20%	NR	47.80%	NR	94.50%
Kaddu-Mulindwa et al., 2021 [16]	NHL	n = 930	38.00%	84.00%	100%	100%	100%	100%	84.00%	95.00%
Göçer et. al., 2021 [17]	FL	n = 46	NR	31.50%	NR	85.10%	NR	60.00%	NR	63.80%
	DLBCL	n = 127	NR	36.80%	NR	96.30%	NR	63.60%	NR	89.60%
	NHL	n = 58	NR	52.90%	NR	87.50%	NR	85.70%	NR	56.70%
Maisarah et al., 2021 [18]	DLBCL	n = 21	NR	100%	NR	77.80%	NR	42.90%	NR	100%
Lim et al., 2021 [19]	DLBCL	n = 512	NR	59.30%	NR	93.60%	NR	54.70%	NR	94.60%
Nakajima et al., 2020 [20]	FL	n = 261	NR	57.00%	NR	82.00%	NR	59.00%	NR	81.00%
St-Pierre et al., 2020 [21]	FL	n = 548	NR	60.00%	NR	80.00%	NR	NR	NR	NR
Al-Sabbagh et al., 2020 [22]	Aggressive	n = 89	50.00%	95.83%	100%	100%	100%	100%	84.42%	98.48%
Kandeel et al., 2020 [23]	DLBCL	n = 88	68.80%	66.70%	100%	89.70%	100%	76.90%	84.90%	83.90%
Kupik et al., 2020 [24]	NHL	n = 89	81.60%	69.00%	100%	100%	100%	100%	89.00%	80.00%
Elamir et al., 2020 [25]	NHL	n = 57	53.60%	96.40%	100%	100%	100%	100%	69.00%	96.70%
	DLBCL	n = 27	53.30%	100%	100%	100%	100%	100%	63.20%	100%
Büyükşimşek et al., 2020 [26]	NHL	n = 269	55.00%	65.00%	NR	NR	NR	NR	73.40%	78.00%
	DLBCL	n = 186	47.00%	72.30%	NR	NR	NR	NR	70.10%	81.70%
	FL	n = 34	60.00%	66.70%	NR	NR	NR	NR	75.00%	78.30%
	MCL	n = 24	85.70%	42.90%	NR	NR	NR	NR	83.30%	55.60%
	BL	n = 12	66.70%	33.30%	NR	NR	NR	NR	88.90%	80.00%
	PMBCL	n = 13	66.70%	33.30%	NR	NR	NR	NR	90.90%	83.30%
Tezol et al., 2020 [27]	NHL	n = 20	NR	50.00%	NR	50.00%	NR	60.00%	NR	40.00%
Yang et al., 2020 [28]	MCL	n = 39	NR	77.78%	NR	86.67%	NR	87.50%	NR	76.47%
Xiao Xue et al., 2011 [29]	DLBCL	n = 55	NR	77.80%	NR	89.10%	NR	NR	NR	NR
Yağci-Küpeli et al., 2019 [30]	NHL	n = 36	58.30%	75.00%	95.80%	100%	100%	100%	82.10%	88.90%
Chen et al., 2019 [31]	NHL	n = 46	39.00%	100%	100%	100%	NR	NR	NR	NR
Abe et al., 2019 [32]	PTCL	n = 83	60.70%	89.30%	100%	100%	100%	100%	83.30%	94.80%
Badr et al., 2018 [33]	NHL	n = 27	35.89%	100%	100%	98.00%	100%	95.10%	80.20%	100%
Özpolat et al., 2018 [34]	NHL	n = 22	NR	75.00%	NR	64.00%	NR	57.00%	NR	95.00%
Chen et al., 2018 [35]	NHL	n = 93	56.00%	95.00%	100%	98.00%	100%	97.00%	74.00%	96.00%
Öner et al., 2017 [36]	NHL	n = 108	NR	24.32%	NR	90.14%	NR	56.25%	NR	69.57%
Teagle et al., 2017 [37]	DLBCL	n = 24	NR	100%	NR	100%	NR	100%	NR	100%
	FL	n = 12	NR	0%	NR	72.70%	NR	0%	NR	88.90%
Albano et al., 2017 [38]	NHL	n = 57	NR	50.00%	NR	84.40%	NR	36.40%	NR	90.50%
Pham et al., 2017 [39]	NHL	n = 16	NR	20.00%	NR	66.70%	NR	NR	NR	NR
El Karak et al., 2017 [40]	DLBCL	n = 54	NR	80.00%	NR	80.00%	NR	33.00%	NR	98.00%
Yilmaz et al., 2017 [41]	DLBCL	n = 201	NR	91.30%	NR	94.30%	NR	67.70%	NR	98.80%
Vishnu et al., 2017 [42]	DLBCL	n = 99	NR	86.00%	NR	86.00%	NR	50.00%	NR	98.00%

Table 3. *Cont.*

Reference	NHL Subtype		Sensitivity		Specificity		PPV		NPV	
			BMB	PET/CT	BMB	PET/CT	BMB	PET/CT	BMB	PET/CT
Alzahrani et al., 2016 [43]	NHL	n = 530	NR	60.00%	NR	79.00%	NR	36.00%	NR	91.00%
	DLBCL	n = 48	NR	77.00%	NR	79.00%	NR	29.00%	NR	97.00%
Chen-Liang et al., 2015 [44]	NHL	n = 232	77.60%	52.70%	NR	NR	NR	NR	90.20%	81.70%
	DLBCL	n = 155	62.50%	65.60%	NR	NR	NR	NR	91.10%	91.70%
	BL	n = 9	66.70%	83.30%	NR	NR	NR	NR	60.00%	75.00%
	FL	n = 41	93.70%	50.00%	NR	NR	NR	NR	96.10%	75.80%
	MCL	n = 27	95.20%	28.60%	NR	NR	NR	NR	87.70%	28.60%
Kim et al., 2015 [45]	Indolent	n = 11	NR	0%	NR	100%	NR	0%	NR	64.00%
	Aggressive	n = 75	NR	61.00%	NR	96.00%	NR	85.00%	NR	89.00%
Lee et al., 2015 [46]	Indolent	n = 46	96.00%	84.00%	100%	95.00%	100%	95.00%	95.00%	83.00%
Adams et al., 2015 [47]	DLBCL	n = 40	NR	14.30%	NR	100%	NR	NR	NR	NR
Çetin et al., 2015 [48]	Aggressive	n = 100	NR	51.70%	NR	83.00%	NR	55.50%	NR	80.80%
Cortés-Romera et al., 2014 [49]	DLBCL	n = 84	NR	94.00%	NR	87.00%	NR	63.00%	NR	98.00%
Adams et al., 2014b [50]	DLBCL	n = 78	NR	68.80%	NR	NR	NR	NR	NR	NR
Adams et al. 2014c [51]	FL	n= 22	NR	85.70%	NR	87.50%	NR	NR	NR	NR
Berthet et al., 2013 [52]	DLBCL	n = 133	24.20%	93.90%	100%	99.00%	100%	96.90%	80.00%	98.00%
Khan et al., 2013 [53]	DLBCL	n = 130	40.00%	94.00%	100%	100%	NR	NR	NR	NR
Pelosi et al., 2011 [54]	Aggressive	n = 207	67.80%	64.40%	NR	NR	NR	NR	NR	NR
	DLBCL	n = 120	40.00%	84.00%	NR	NR	NR	NR	NR	NR
	MCL	n = 7	100%	16.50%	NR	NR	NR	NR	NR	NR
	FL	n = 48	81.00%	61.90%	NR	NR	NR	NR	NR	NR
Mittal et al., 2011 [55]	NHL	n = 77	82.00%	88.00%	NR	95%	NR	93.00%	91.30%	100%
	Aggressive	n = 60	76.00%	100%	NR	94%	NR	93.00%	85.30%	100%
	Indolent	n = 17	100%	50.00%	NR	100%	NR	100%	100%	70.00%

3.3. Methodological Quality Assesment

The QUADAS-2 test scores of the 41 included studies are summarized in Table 4. Patient selection was assessed with an unclear risk of bias in 20 of the included studies because the participants sample was unclearly defined as to whether selection was random or consecutive. For the index test, only one of the included studies [26] were assessed with an unclear risk of bias, due to insufficient reporting of results of the index test if they were interpreted with or without a knowledge of reference standard findings. In the reference standard domain, four studies had an unclear risk of bias because of poorly reporting if the reference standard were interpreted without knowledge about the index test findings. Lastly, for the flow and timing assessment, five studies were evaluated with high risk of bias because the time interval between the index test and reference standard was 30 days and above which might affect the accuracy of the results and, in 15 of the 41 included studies, it was assessed with unclear risk of bias due to failing to report the time interval between the index test and the reference standard. According to the applicability concerns, all 41 studies were assessed with low risk. All included patients and reference standard were matching the review question. The index test was conducted and interpreted similarly in all the included studies.

Table 4. Quality assessment of the included studies.

Reference	Risk of Bias				Applicability Concerns		
	Patients Sample	Index Test	Reference Standard	Flow and Timing	Patients Sample	Index Test	Reference Standard
Aguado-Vázquez et al., 2021 [15]	L	L	L	UN	L	L	L
Kaddu-Mulindwa et al., 2021 [16]	L	L	L	UN	L	L	L
Göçer et. al., 2021 [17]	L	L	L	L	L	L	L
Maisarah et al., 2021 [18]	L	L	L	UN	L	L	L

Table 4. *Cont.*

Reference	Risk of Bias				Applicability Concerns		
	Patients Sample	Index Test	Reference Standard	Flow and Timing	Patients Sample	Index Test	Reference Standard
Lim et al., 2021 [19]	L	L	L	L	L	L	L
Nakajima et al., 2020 [20]	L	L	L	UN	L	L	L
St-Pierre et al., 2020 [21]	L	L	L	UN	L	L	L
Al-Sabbagh et al., 2020 [22]	L	L	L	L	L	L	L
Kandeel et al., 2020 [23]	L	L	L	L	L	L	L
Kupik et al., 2020 [24]	UN	L	L	UN	L	L	L
Elamir et al., 2020 [25]	UN	L	L	L	L	L	L
Büyükşimşek et al., 2020 [26]	UN	UN	UN	L	L	L	L
Tezol et al., 2020 [27]	UN	L	L	UN	L	L	L
Yang et al., 2020 [28]	UN	L	L	UN	L	L	L
Xiao Xue et al., 2020 [29]	UN	L	L	L	L	L	L
Yağci-Küpeli et al., 2019 [30]	UN	L	L	UN	L	L	L
Chen et al., 2019 [31]	L	L	UN	UN	L	L	L
Abe et al., 2019 [32]	L	L	L	UN	L	L	L
Badr et al., 2018 [33]	UN	L	L	L	L	L	L
Özpolat et al., 2018 [34]	UN	L	L	UN	L	L	L
Chen et al., 2018 [35]	L	L	L	L	L	L	L
Öner et al., 2017 [36]	UN	L	L	L	L	L	L
Teagle et al., 2017 [37]	UN	L	L	H	L	L	L
Albano et al., 2017 [38]	UN	L	L	L	L	L	L
Pham et al., 2017 [39]	UN	L	UN	H	L	L	L
El Karak et al., 2017 [40]	L	L	L	UN	L	L	L
Yilmaz et al., 2017 [41]	UN	L	L	L	L	L	L
Vishnu et al., 2017 [42]	L	L	L	L	L	L	L
Alzahrani et al., 2016 [43]	UN	L	L	UN	L	L	L
Chen-Liang et al., 2015 [44]	L	L	UN	H	L	L	L
Kim et al., 2015 [45]	UN	L	L	UN	L	L	L
Lee et al., 2015 [46]	L	L	L	L	L	L	L
Adams et al., 2015 [47]	L	L	L	L	L	L	L
Cetin et al., 2015 [48]	L	L	L	UN	L	L	L
Cortés-Romera et al., 2014 [49]	UN	L	L	L	L	L	L
Adams et al., 2014b [50]	UN	L	L	L	L	L	L
Adams et al., 2014c [51]	L	L	L	L	L	L	L
Berthet et al., 2013 [52]	L	L	L	H	L	L	L
Khan et al., 2013 [53]	UN	L	L	H	L	L	L
Pelosi et al., 2011 [54]	L	L	L	L	L	L	L
Mittal et al., 2011 [55]	UN	L	L	L	L	L	L

(L) Low risk of bias, (H) High risk of bias, (UN) Unclear.

3.4. Diagnostic Performance of PET/CT and BMB in Determining BMI

This systematic review included studies with a total of 6147 patients diagnosed with NHL. Some studies did not report the number of the male and female patients. Among the studies that mentioned this information, 3025 were male and 2344 female patients. Only some studies reported the number of the patients for each lymphoma stage, which was as follows: stage I, stage II, stage III, stage IV. From all these, the total number of patients for each stage was as following: stage I 277 patients, stage II 407 patients, stage III 609 patients, stage IV 1011 patients. Some studies [16,19,43,50] reported the number of the patients as stage (I and II) and stages (III and IV) together as follows: in Kaddu-Mulindwa et al. [16] study (n = 501) patients classified in stages (III–IV); in Lim et al. [19] (n = 285) patients

classified in stages (I–II); in Alzahrani et al. [43] (n = 197) patients classified in stages (I–II) and (n = 333) patients classified in stages (III–IV); in Adams et al. [50] (n = 60) patients classified in stages (III–IV). The remaining studies did not report the number of the patients for each stage.

3.4.1. Diagnostic Performance of [^{18}F]FDG PET/CT and BMB in Determining BMI in NHL Patients

Among the included studies, the median values for sensitivity, specificity, PPV and NPV of [^{18}F]FDG PET/CT and BMB were analyzed and presented in Table 5. For the general population of NHL, the sensitivity and specificity of [^{18}F]FDG PET/CT in determining BMI ranged from 0% to 100% (median = 73.30%) and from 50% to 100% (median = 89.70%) across the eligible studies, respectively. Moreover, the PPV and NPV of [^{18}F]FDG PET/CT in determining BMI for NHL patients ranged from 0% to 100% (median = 63.30%) and from 56.70% to 100% (median = 92.45%), respectively. For the BMB analysis of the NHL cases, the sensitivity ranged from 24.00% to 96% (median = 56.00%), the specificity ranged from 95.80% to 100% (median = 100%), the PPV 100% (median = 100%), NPV ranged from 69% to 95% (median = 83.65%).

Table 5. Diagnostic performance of [^{18}F]FDG PET/CT and BMB in determining BMI in NHL cases and subtypes of NHL lymphoma cases.

		Sensitivity (Median)		Specificity (Median)		PPV (Median)		NPV (Median)	
No. Studies	**Disease**	**[^{18}F]FDG PET/CT**	**BMB**	**[^{18}F]FDG PET/CT**	**BMB**	**[^{18}F]FDG PET/CT**	**BMB**	**[^{18}F]FDG PET/CT**	**BMB**
20	DLBCL	77.40%	47.00%	91.65%	100.00%	63.60%	100.00%	97.00%	80.00%
9	FL	60.00%	81.00%	81.00%	NR	59.50%	NR	79.65%	85.55%
4	MCL	60.34%	95.20%	86.67%	NR	87.50%	NR	55.60%	71.65%
2	BL	58.30%	66.70%	NR	NR	NR	NR	77.50%	73%
1	PMBCL	33.30%	66.70%	NR	NR	NR	NR	83.30%	90.90%
1	PTCL	89.30%	60.70%	100%	100%	100%	100%	94.80%	83.30%
41	NHL	73.30%	56.00%	89.70%	100.00%	63.30%	100.00%	92.45%	83.65%
12	Indolent	58.50%	93.70%	85.10%	100.00%	60.00%	100.00%	78.30%	95.55%
24	Aggresive	77.00%	57.90%	93.80%	100.00%	63.60%	100.00%	97.00%	84.42%

NR = not recorded.

Among the included studies with patients data of indolent NHL for [^{18}F]FDG PET/CT (n = 1164; studies = 12), the median values of the sensitivity, specificity, PPV and NPV were 58.50%, 85.10%, 60.00%, 78.30%, respectively. For the studies of BMB with patients data of indolent NHL (n = 186; studies = 5), the median sensitivity and NPV was 93.70% and 95.55%, while the specificity and PPV were reported only on one study [46] and were equal with 100%. Regarding the studies with patient populations with aggressive NHL for [^{18}F]FDG PET/CT (n = 2821; studies = 24), the median sensitivity was 77.00%, specificity 93.80%, PPV 63.60%, and NPV 97.00%. For the included studies with patients data of aggressive NHL for BMB (n = 1216; studies = 9), the median sensitivity was 57.90% and NPV 84.42%, whereas the specificity and PPV were calculated only in five and four of the studies, respectively, and they were both equal to 100%.

3.4.2. Diagnostic Performance of [^{18}F]FDG PET/CT and BMB in Determining BMI in Subtypes Lymphoma

According to the studies included in this systematic review, the overall sensitivity, specificity, PPV, NPV of [^{18}F]FDG PET/CT and BMB were analyzed for different subtypes of lymphoma cases. For DLBCL, across the eligible studies, the sensitivity of [^{18}F]FDG PET/CT in determining BMI (n = 2336; studies = 20) ranged from 14.10% to 100% (median = 77.40%), specificity ranged from 54% to 100% (median = 91.65%), PPV ranged from 29.00% to 100% (median = 63.60%), and NPV ranged from 81.00% to 100%

(median = 97.00%). For DLBCL, the sensitivity of BMB in determining BMI ranged from 24.00% to 68.80% (median = 47.00%), specificity was 100%, PPV was 100% and NPV ranged from 63.20% to 91.10% (median = 80.00%).

For the subtype FL, the sensitivity of [^{18}F]FDG PET/CT in determining BMI (n = 1059; studies = 9) ranged from 0% to 86.00% (median = 60.00%), specificity ranged from 72.70% to 88.00% (median =81.00%), PPV ranged from 0% to 61.10% (median = 59.50%), and NPV ranged from 63.00% to 89.70% (median = 79.65%). Compared to BMB, for the subtype FL the sensitivity of [^{18}F]FDG PET/CT ranged from 0% to 81.00% (median = 58.50%) while for BMB ranged from 60.00% to 93.70% (median = 81.00%).

For MCL cases, the sensitivity and NPV of [^{18}F]FDG PET/CT in determining BMI (n = 97; studies = 4) ranged from 28.60% to 100% (median = 60.34%) and 28.60% to 76.47% (median = 55.60%), respectively. For BMB, the sensitivity and NPV ranged from 42.90% to 100% (median = 95.20%) and 55.60% to 87.70% (median = 71.65%), respectively. For BL cases, the sensitivity of [^{18}F]FDG PET/CT in determining BMI (n = 21; studies = 2) ranged from 33.30% to 83.30% whereas for the BMB it was 66.70%. The NPV for [^{18}F]FDG PET/CT ranged from 75.00% to 80.00% and the BMB ranged from 60.00% to 88.90%. The specificity and PPV were not reported in any of the studies.

4. Discussion

This systematic review included 41 studies that included a total of 6147 newly diagnosed NHL patients. All patients underwent both [^{18}F]FDG PET/CT and BMB to diagnose the involvement of the bone marrow. Most of the patients were classified as stage IV according to the Ann Arbor staging system. Overall, the included studies were of high quality with few methodological concerns in the outcome measurements.

The results of this systematic review showed that [^{18}F]FDG PET/CT achieves a high specificity (90%) but a moderate sensitivity (73%) in detecting bone marrow involvement in newly diagnosed NHL patients. Our results regarding the diagnostic performance of PET/CT are not in full agreement with the previous systematic review by Pakos et al., [14], which found lower sensitivity (43%) and similar specificity (88%). However, Pakos et al., [14] only included three studies with a mixed population of a total of 239 NHL patients, whereas our investigation includes 41 studies with a total of 6147 NHL patients. The larger sample size of our study also included more patients with various bone marrow involvement, making the generalisations more robust. Another difference between our systematic review and Pakos et. al. [14], is that they investigated single PET units, whereas our paper considers studies including only PET/CT. However, previous studies have shown that although PET/CT has higher sensitivity in detecting bone marrow infiltration compared to a single PET unit, their differences are not expected to be statistically significant [56]. When [^{18}F]FDG PET/CT was compared with the BMB, which is the traditional method used for determining the BMI in NHL patients, we found that the [^{18}F]FDG PET/CT achieves a higher sensitivity than BMB. More specifically, BMB achieves a sensitivity of 56%, whereas [^{18}F]FDG PET/CT achieves a sensitivity of 73%. The lower sensitivity of BMB compared to [^{18}F]FDG PET/CT indicates that biopsy in the iliac crest area may miss bone marrow involvement that can be found by the [^{18}F]FDG PET/CT.

In addition, if a PET/CT scan is positive, bone marrow involvement can be excluded with high certainty and BMB may be avoided. On the other hand, if a [^{18}F]FDG PET/CT is negative a BMB should be performed as we cannot exclude the presence of BMI. A blind BMB was recommended for all DLBCL patients from the European Society for Medical Oncology (ESMO) until 2015 when new guidelines were published [57] advising that BMB is not required when there is a positive PET/CT for bone marrow involvement. However, a BMB is required in case of negative PET, when its results would change prognosis and treatment, especially if a shortened number of immunochemotherapy cycles is proposed. On the basis of these findings, a blind BMB in all NHL for staging purposes needs to be re-evaluated. The results of our study might impact on the guidelines for the general population of NHL patients since it is still not clear whether biopsy is or not required.

The patient population of this systematic review was separated based on the different subtypes of NHL. For the mixed population of indolent NHL the results of this review indicated that BMB is far more sensitive in indolent NHL than [^{18}F]FDG PET/CT and thus it is not recommended to replace the routine BMB with PET/CT for identifying BMI in such patients, as many cases will be missed. For less aggressive or indolent lymphomas 11C-Acetate PET/CT might be a promising approach although it requires further evaluation as it has been found to achieve a higher sensitivity compared to the [^{18}F]FDG PET/CT [58]. The largest percentage (about 70%) of all indolent lymphomas worldwide are FL [59]. FL is also the second most common subtype of NHL. For patient cases with FL disease, across the studies investigated in this review, the sensitivity of BMB compared to [^{18}F]FDG PET/CT in determining BMI was superior. FL is highly variable in terms of presentation of the disease. Although most of the patients have a good prognosis with a standard treatment, and experience remission of the disease, some of them may experience relapse of the disease after the first line of treatment. FL is characterized by a high probability of BMI, and at least 70% of the patients have BMI, whereas the involvement of other organs is infrequent. Factors such as BMI can help identify disease extension and identify patients who may experience clinical failure and adjust therapeutic strategy accordingly. The results of this study demonstrate that the most reliable method to determine BMI in these patients remains the BMB. However, [^{18}F]FDG PET/CT can be used as a complementary method.

In contrast, when aggressive types of NHL were investigated, our results demonstrated that the [^{18}F]FDG PET/CT achieves moderate sensitivity and high specificity. [^{18}F]FDG PET/CT is a more sensitive method for detecting BMI compared to the BMB. Both the sensitivity and specificity of [^{18}F]-PET/CT is higher for patients with aggressive NHL compared with patients with indolent NHL. The [^{18}F]FDG PET/CT showed higher diagnostic accuracy for the assessment of aggressive NHL patients than indolent histologic subtypes of NHL, probably due to the high metabolic activity of the aggressive tumors. In highly aggressive subtypes, it is even more important to identify the extent of the disease as early as possible. When separating the population and investigating the most common aggressive subtype of NHL, DLBCL, from all eligible studies the sensitivity and specificity of FDG PET/CT in determining BMI was 77% and 92%, respectively. A previous meta-analysis conducted by Adams et al. [11] in a study with a much smaller sample size, the authors found a higher sensitivity (88.7%) and specificity (99.8%) for [^{18}F]FDG PET/CT in detecting BMI in DLBCL patients compared to our results. As a result of the presented findings, a combination of [^{18}F]FDG PET/CT and BMB are be useful for improving the accuracy of BMI assessment and reducing the sampling error issue of BMB.

This systematic review involved some limitations. In some studies PET/CT images were interpreted using qualitative criteria [15–17,19,20,22,26,29,31,34–39,42,43,47,48,50,52–54], whereas in other studies both qualitative and quantitative criteria were used [18,21,23–25,27,28,30,32,33,40,41,44–46,49,51,55]. As the qualitative evaluation is based on a subject's experience, this might underestimate the PET/CT diagnostic performance. Quantification using PET/CT images has shown improvement in the prediction of BMI compared to a qualitative analysis [51]. In addition, an even more improved prediction of BMI might be feasible with the use of radiomics that extract quantitative markers. The role of radiomic features in extracting useful information for diagnosis via BMI [^{18}F]FDG PET/CT images has been shown in recent studies for the MCL [60] and DLBCL [61]. PET/MRI can also be used as a better predictor of BMI compared to BMB for NHL [62]. Compared with PET/CT, it is expected that PET/MRI can provide comparable detectability for lymphoma imaging [63,64]. Other factors that might affect the results include region-specific and genetics-related differences; however, it was not possible to investigate these factors with the given data. The pattern and degree of bone marrow metabolic activity changes with age and FDG distribution is consequently affected. Previous studies have already concluded that SUV_{max} in bone marrow is decreases with aging [65,66]; therefore, differences among some studies evaluating PET/CT for BMI may be explained by possible variations in population ages in the samples used. However, the studies included in this review do not provide sufficient evidence to derive conclusions on how age-related

changes might affect PET/CT performance. Lastly, this systematic review included patients who were newly diagnosed with NHL. In clinical scenarios [^{18}F]FDG PET/CT might show a lower specificity in patients with infection, inflammation or after chemotherapy is expected to have highly FDG-avid regions, which might result in a false positive interpreted as the BMI. Special care should be taken with regard to these patients when deciding if BMB should be avoided or not.

5. Conclusions

This systematic review assessed the summary estimates of the diagnostic performance of [^{18}F]FDG PET/CT and BMB to detect BMI in NHL patients. In aggressive NHL, [^{18}F]FDG PET/CT has high sensitivity and specificity and BMB may be avoided. In indolent NHL, [^{18}F]FDG PET/CT has low sensitivity and only BMB has a prognostic value. However, [^{18}F]FDG PET/CT might be used as a complementary method to BMB to enhance the retrieval of diagnostic information for BMI detection.

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