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Original Article

A 10-point scoring system for evaluation of breast cancer based on 5-year survival

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Abstract: *Objectives*: Quantifying malignancy is difficult. The present study establishes a 10-point scoring system for breast cancer, which directly reflects the chances of 5-year survival. *Methods*: The 10-point scoring system was based on 5-year overall survival (5Y-OS). The score was set "0" if the 5Y-OS is 100%, and "10" in the case of 0%. The histological types, histological grades, TNM stages, and molecular types were scored separately based on the available literature. The specific score for each index was calculated based on meta-analysis of a cluster of 128 articles obtained from PubMed and CNKI database of China. A final combined score was calculated. *Results*: Twenty-three histological types of breast cancers were scored between 0 and 6.68 and classified into 4 prognosis groups, such as excellent, good, low-moderate, and poor prognosis. The non-special type (NST) was further scored by histological grade, in a range of 1.12-3.95. Five stages based on TNM were scored as 0.5-6.49. Four molecular types were scored between 1.0 and 2.69. The weight in the combined score was based on the differential capacity. For NST type, TNM staging, histological grade, and molecular type were 0.6, 0.25, and 0.15, respectively. For special types, the histological type and TNM stage each received a score of 0.5. The final score of the excellent prognosis group was 0. *Conclusion*: The present study established a 10-point scoring system, which could be utilized pathologically.

Keywords: Breast cancer, prognosis, score system, histological types, histological grades, TNM stages, molecular types

Introduction

Tumors are classified as benign and malignant. In the case of benign tumors, it is not essential to designate their degree. Nevertheless, for malignant tumors, it is desirable to quantify their malignant potential. Currently, although cancers are typically described as low malignant, moderate malignant, to highly malignant, the definition is vague, thus rendering it difficult to determine the degree of malignancy. Therefore, to provide an accurate characterization by quantification and accuracy, we set up a scoring system, which directly reflects the survival chance of the cancer patients.

Breast cancer is the most common malignant tumor in women worldwide. Since the 1980s, the incidence and mortality of breast cancer have constantly been increasing. In comparison to that in 2008, the incidence and the mortality rose by 20% and 14%, respectively [1]. Breast cancer is highly heterogeneous, not only histologically but also at the molecular level. According to the WHO classification, there are 26 histological types and 5 molecular types of breast cancers. Since it is clear that all the breast cancers are not of the same malignancy, the patient should be treated differently, using the novel concept of precision medicine. A prerequisite of precision medicine is to precisely evaluate the malignancy of cancer and the prognosis of the patient. In breast cancer, the TNM staging and Nottingham Prognostic Index (NPI) are the two most common evaluation criteria of prognosis. The latter combines both the tumor size, nodal status, and the histological grade, and can provide a relatively accurate prognosis of the breast cancer patients [2]. However, since it was designed three decades

Table 1. Scores of different histological types of breast cancer

Histological Type	Cases	5Y-OS (%)	Score
Excellent			
DCIS	2447	100	0
LCIS	214	100	0
MEC	13	100	0
IDPC	311	100	0
EPC	305	100	0
Good			
CC	259	98.06	0.19
ACC	696	96.26	0.37
TC	743	95.82	0.42
SPC	139	95.65	0.43
MDC	218	94.57	0.54
MC	13246	93.74	0.63
Moderate			
SC	83	87.2	1.28
ILC	500319	87.08	1.29
NST	1008497	82.22	1.78
IMPC	1475	80.96	1.90
IPC	1278	79.2	2.08
PD	458	78.79	2.12
GRCC	20	75	2.50
Poor			
MBC	1068	68.8	3.12
MPC	1620	62.98	3.70
NET	607	60.61	3.94
IBC	10397	54.9	4.51
LRC	49	33.2	6.68

Abbreviations: DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; MEC, mucoepidermoid carcinoma; IDPC, intraductal papillary carcinoma; EPC, encapsulated papillary carcinoma; CC, cribriform carcinoma; ACC, adenoid cystic carcinoma; TC, tubular carcinoma; SPC, solid papillary carcinoma; MDC, medullary carcinoma; MC, mucous carcinoma; SC, secretory carcinoma; ILC, invasive lobular carcinoma; NST, non-special type; IMPC, invasive micropapillary carcinoma; IPC, Invasive papillary carcinoma; PD, Paget's disease; GRCC, Glycogen-rich clear cell carcinoma; MBC, male breast cancer; MPC, metaplastic breast carcinoma; NET, neuroendocrine tumor; IBC, inflammatory breast cancer; LRC, lipid-rich carcinoma.

ago [3], molecular typing information is not included. Moreover, the Nottingham scoring system is difficult for patients to understand.

Herein, we aimed to establish an evaluation system for cancer, based on 10-point scores. Since data on breast cancer are most abundant, along with existing scoring systems as a reference, we used breast cancer to establish this scoring model. The system was combined with indexes of histopathology, TNM staging, and molecular typing. Furthermore, the system was designed to predict using pathology, the malignancy of cancer, its TNM stage, molecular characteristics, and the chance of 5-year survival. Such a report would provide the physicians a clearer picture of cancer, thereby instigating improved communication with the patient. A patient-oriented, suitable treatment decision could be made based on such a scoring system.

Methods

Design of the evaluation system

The system was designed as a 10-point scoring system based on the 5-year overall survival (5Y-OS). If the 5Y-OS was 0%, a score of "10" was assigned. If the 5Y-OS was 100%, then a score of "0" was allocated. Each TNM stage, histological type, histological grade, and molecular type was also assigned a score based on the evaluation of literature. To give a combined score, the weight of TNM stage, histopathology, and molecular typing were decided based on their capacity of prognostication. The combined prognostic score yielded by the system was based on each specific score and the weight of each part.

Data search

A comprehensive and computerized literature search was carried out on PubMed and China National Knowledge Infrastructure (CNKI) from the beginning of indexing to June 2015. The terms (survival OR prognosis OR 5Y-OS) AND (invasive ductal cancer OR invasive lobular cancer OR mucinous breast cancer OR TNM stage OR grade OR molecular type) were used to search for relevant data. All available 5Y-OS were collected and classified by evaluation indexes (Supplementary Tables 1, 2, 3, 4). Altogether, 135 articles and 1398169 cases were used for survival analysis and establishing the system.

Data analysis

To determine a specific score for different TNM staging, histological type and grade, and molec-

Table 2. Scores of different histological grades of NST breast cancer

Grade	Cases (%)	5Y-OS	Score
G1	1136 (17)	88.78%	1.12
G2	2822 (43)	74.66%	2.53
G3	2537 (40)	60.50%	3.95

Table 3. Scores of different TNM stages of breast cancer

Stage	Cases (%)	5Y-OS	Score
0	86 (0.03)	95%	0.50
I	137536 (51.0)	94.04%	0.60
II	113801 (42.3)	79.78%	2.02
III	17036 (6.4)	62.71%	3.73
IV	997 (0.3)	35.15%	6.49

Table 4. Scores of different molecular types of breast cancer

Type	Cases (%)	5Y-OS	Score
Luminal A	14927 (55)	89.99%	1.00
Luminal B	3395 (12)	84.9%	1.51
HER2	3149 (11)	76.13%	2.39
TNBC	5874 (22)	73.37%	2.66

ular type, meta-analyses were conducted with each category from the mined data. The 5Y-OS correlated with every evaluation sub-index were calculated according to the proportion of cases in each study to the total number of cases for every evaluation index. The formula was used to estimate the final score of each sub-index.

Calculation of the combined score

The final combined score was calculated by assigning different weights to the histological types, grades, TNM stages, and molecular types. The weight varies in different histological types and was decided by the predicting power of these indexes, i.e. the difference between the highest score and the lowest score. The formula is $Wx = dx/(d1+d2+d3)$.

Results

Scores based on the histopathology

Histopathology is the foundation of cancer pathology. There were approximately 23 histological types of breast cancer including 2 types of debatable in situ carcinomas. First, we collected a total of 1094462 cases of breast cancer from 92 articles and performed a meta-analysis of the 5Y-OS of each histotype. A score was assigned to each type of breast cancer inversely proportional to the survival chance, ranging from 0-6.68. Two types of *in situ* carcinoma, i.e., ductal carcinoma *in situ* (DCIS) and lobular carcinoma *in situ* (LCIS), and mucoepidermoid carcinoma (MEC), intraductal papillary carcinoma (IDPC), encapsulated papillary carcinoma (EPC) were all scored 0, with a 5Y-OS of 100%. The histotype with the highest score was lipid-rich clear cell carcinoma (LRCCC) with a score of 6.68; its 5Y-OS was only 33.2% (**Table 1**).

Of the 23 histological types, the non-special type (NST) was the largest category, accounting for around 70% of all the breast cancer cases. Furthermore, it was also a rather heterogeneous entity. These were typically divided into three histological grades based on the differentiation, features of cell nuclei, and cell proliferation ratio. Accordingly, we also conducted a meta-analysis on the survival of different grades of NST breast cancer, and specific scores were assigned according to their 5Y-OS (**Table 2**).

This scoring system provided us an outline of the different histological types of breast cancer. We then categorized them into 4 groups, i.e., excellent prognosis, good prognosis, low moderate prognosis, and poor prognosis. The excellent prognosis group included those that scored 0, the good prognosis group included those that scored between 0-1, the low-moderate group included those that scored 1-3, and the poor prognosis group included those that scored >3.

Scores based on TNM staging

TNM staging is a widely adopted staging system for most types of malignant solid tumors, based on the size of the primary tumor, nodal status, and the prevalence of metastasis to distant organs. In breast cancer, it was divided into five stages, i.e., stage 0, I, II, II, and IV. We extracted 269456 cases of 5Y-OS data in different stages, and their calculated corresponding survival rates were 95%, 94.04%, 79.78%, 62.71%, and 35.15%, respectively. Accordingly,

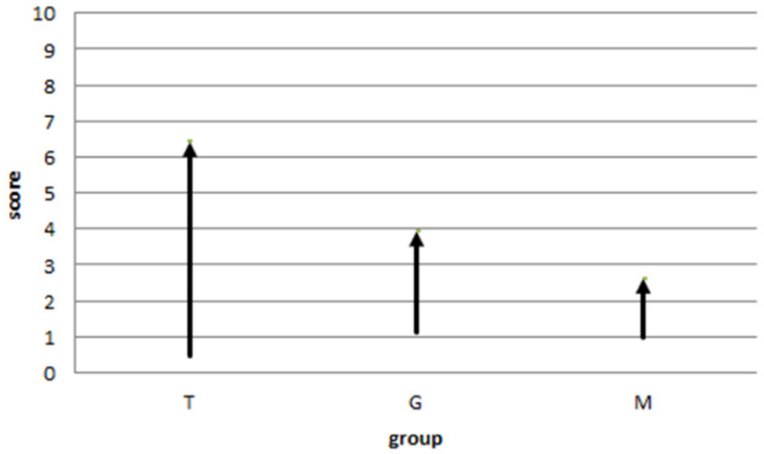

Figure 1. The prognosis power of three indexes of non-special type breast cancer. T stands for TNM; G stands for histological grades; M stands for molecular types. The three are roughly about 6:3:1.5.

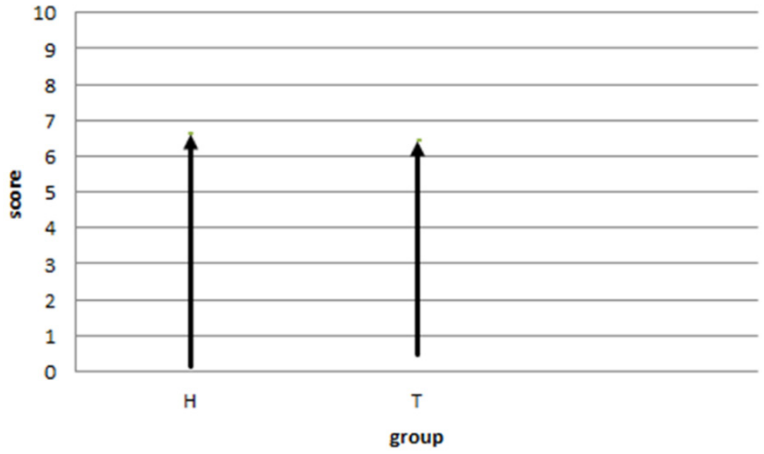

Figure 2. The prognosis power of histological typing (H) and TNM (T) staging in special types of breast cancer. The two are about equal.

the assigned score was 0.5, 0.6, 2.02, 3.63, and 6.49, respectively (**Table 3**).

Scores based on molecular typing

Molecular subtyping has been the most attractive part of cancer pathology in the new century. Breast cancer was classified into four types, i.e., luminal A, luminal B, HER2-positive, and basaloid/triple negative. It is a topic of intensive research with already around 28000 cases of documented survival analysis in the last decade. The three largest data sets, which represent 70% of all the cases were from Korea. The corresponding number of cases of the four types were 14927, 3395, 3149, and 5874 respectively, with luminal A type around 55%. Both Luminal B and HER2-positive group showed HER2 amplification. Taken together, these two types accounted for around 23% of all the cases. The triple-negative breast cancer was ascribed as 22%. The 5Y-OS rates were approximately 90%, 84.9%, 76.1%, and 73.4%, respectively. Accordingly, they were assigned scores of 1.0, 1.51, 2.39, and 2.66, respectively (**Table 4**).

The combined score: weight distribution among the sub-indexes

Several parameters were taken into consideration while deciding the weight distribution of the sub-indexes. First, since the 5Y-OS of DCIS, LCIS IDPC, EPC, and MEC patients were all 100%, the final score was only 0, regardless of the tumor size and molecular feature. Second, NST breast cancer was the most prevalent and heterogeneous group. The prognosis of NST varied greatly depending on the TNM stages, histological grades, and the molecular types. Therefore, all the three factors should be taken into account. The weight of each part depends on their differentiation capacity. The score range of the 5 TNM stages was between 0.5 and 6.49, that of the 3 histological grades was between 1.12 and 3.95, while that of the molecular types was between 1.0 and 2.66. The combined difference of the histological grades and molecular types was only 4.49, which was much less than that of the TNM stages (**Figure 1**). Therefore, the weight coefficient was assigned as, TNM stages =0.6, histological grades =0.25, and molecular types =0.15. The third consideration was the special histological types, including all the other 17 types in addition to the first group and NST. This category of breast cancer encompassed about a quarter of all the cases, however their outcomes varied greatly. The histological grading and molecular typing did not

assist in predicting the outcomes of these cases. For example, the cribriform carcinoma, adenoid cystic carcinoma, and tubular carcinoma all had extremely low scores. The histological grading and molecular typing could not add anything to the prognosis of these types. In addition, owing to the low incidence of these special types of breast cancer, little data was available on the survival of these patients with respect to histological grading and molecular typing. Therefore, the combined score of this category of breast cancer was a sole issue between the TNM staging and the histological types. As their differentiation power was in proximity (**Figure 2**), the weight was distributed as, TNM=0.5, histotype =0.5.

Discussion

The present study provides a comprehensive outline of the outcomes of variable breast cancers at different clinical stages and with distinct molecular features. The scoring system established by this study exhibits several advantages as compared to the current prevalent Nottingham prognostic indexes. First, the new system was designed and completed score years later than NPI and was based on abundant comprehensive data. Therefore, it has the later mover advantage. Second, this scoring model was designed as a 10-point system, which directly reflects the 5-year survival chance. Due to its similarity to the routinely used 10-point scoring system of grading aches, it is much easier for the physicians to accept, and thus, simplifying the communication between oncologists and cancer patients. Third, it has a potential to be adapted in the cancers of other organs. Conversely, the NPI indexes, although closely related with prognosis, cannot directly predict the survival chance. Fourth, this system encompasses more comprehensive features of the breast cancer, including histological types, histological grades, molecular types, and TNM staging, which includes tumor size, nodal status, and distant metastasis. Comparatively, NPI only uses histological grades, nodal status, and tumor size as evaluation bases [2].

The present study for the first time set up a queue of malignancy for various histological types of breast cancer according to the 5Y-OS. The scores may help in settling down various controversies including the property of the *in situ* carcinomas and the intracystic papillary carcinoma of the breast. *In situ* carcinomas of different organs, such as cervical carcinoma *in situ*, have been renamed to avoid overtreatment. In recent years, both pathologists and physicians have suggested reconsideration of the definition of cancer, especially the property of ductal carcinoma *in situ* of the breast. Lobular carcinoma *in situ* of the breast has long been recognized as not developing further, and a close follow-up rather than surgical dissection is the principle for the care of LCIS [132]. However, DCIS has been treated more aggressively, including lumpectomy and mastectomy followed by radiotherapy and endocrine therapy. This aggressive treatment may be attributed to the fear that invasive cancer would derive from the *in situ* carcinoma. Interestingly, evidence from molecular pathology, histopathology, and clinical epidemiology all point out that *in situ* carcinoma is not the precursor lesion of invasive breast cancer [133]. Rather, invasive breast cancers may develop *de novo* from misplaced epithelial cells in the stroma [133]. Histologically, the *in situ* carcinomas are devoid of the blood vessel and lymphatics since they are confined to the boundaries within the basement membrane and thus cannot metastasize.

Although molecular typing seems promising for the prediction of prognosis and improving the care of breast cancer and many other malignancies, our analysis from extensive data indicates that histological diagnosis continues to form the basis of cancer biology and should not be overlooked. Comparatively, molecular typing played a minor role in predicting the prognosis of NST breast cancers, with only 15% of weight than the 60% of TNM staging and 25% of histological grading. Nevertheless, this does not exclude the usefulness of molecular typing in designing the molecular targeted therapies, which have benefited a huge population of patients with breast cancer and several other malignant tumors. On the other hand, however, TNM staging and histological typing should not be ignored, and considered pivotal in structuring the treatment strategy for individual case.

However, it should be noted that although this study was based on a plethora of data published worldwide over an extended period, the prediction of the system could be skewed due

to the advancement of cancer care, including early detection and technological improvement. Accordingly, the system awaits further adjustment by cohort studies. Additionally, patients in different countries or various ethnic backgrounds may also lead to different predictions.

In summary, we have established a 10-point evaluation system of breast cancer based on extensive data of 5Y-OS survival. The system is expected to play a role in helping physicians and patients in understanding the state of the disease, and making proper treatment decisions. However, the system awaits further evaluation for clinical applicability.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. 5Y-OS of different histological types of breast cancer

Histological Type	5Y-OS (Cases)
NST/IDC	84.1% (45169) [4], 80.5% (297735) [5], 87.95% (300) [6], 80% (43587) [7], 92.4% (475) [8], 94.9% (2455) [9], 90% (445) [10], 84% (24834) [11], 84% (247583) [12], 70% (912) [13], 95.8% (5707) [14], 87.8% (816) [15], 82% (338479) [16].
Invasive lobular ca (ILC)	87.4% (1051) [17], 85.6% (4140) [4], 94% (65) [10], 87% (43690) [12], 93% (112) [13], 94.6% (851) [14], 94% (57) [18], 88.4% (269) [15], 93.7% (74) [19].
Tubular ca (TC)	100% (83) [14], 94% (444) [7], 97% (146) [20], 100% (70) [21].
Cribriform ca (CC)	98% (250) [14], 100% (9) [22].
Medullary ca (MDC)	100% (61) [23], 85% (33) [24], 88.4% (26) [25], 94.9% (46) [26], 97.1% (52) [27].
Metaplastic ca (MPC)	34.5% (29) [28], 68% (29) [29], 55% (37) [30], 63.3% (1501) [31], 83% (24) [32].
Mucinous ca (MC)	91.3% (88) [33], 90% (1221) [7], 94% (11422) [16], 98.9% (268) [9], 93.5% (104) [34], 96.3% (143) [14].
Neuroendocrine tu (NET)	85.1% (107) [8], 67.6% (74) [35], 53.6% (142) [36], 62.4% (148) [37], 68.9% (42) [37], 32.2% (73) [37], 24.8% (24) [37].
Invasive papillary ca (IPC)	92.77% (284) [6], 89.09% (23) [38], 75% (971) [39].
Invasive micropapillary ca (IMPC)	82.9% (636) [5], 59% (100) [40], 83.8% (624) [41], 67.7% (62) [42], 81.1% (53) [43].
Adenoid cystic ca (ACC)	85% (28) [44], 95.6% (244) [45], 94% (61) [46], 98.1% (338) [47], 96% (25) [48].
Mucoepidermoid ca (MEC)	100% (5) [49], 100% (7) [50], 100% (1) [51].
Intraductal papillary ca (IDPC)	100% (3) [52], 100% (22) [53], 100% (9) [54], 100% (43) [55], 100% (234) [56].
Encapsulated papillary ca (EPC)	100% (20) [57], 100% (2) [58], 100% (208) [59], 100% (1) [60], 100% (39) [61], 100% (21) [62], 100% (14) [54].
Solid papillary ca (SPC)	100% (30) [54], 100% (20) [63], 100% (21) [64], 100% (11) [65], 89.4% (57) [66].
Inflammatory breast ca (IBC)	55.4% (10197) [67], 57% (24) [68], 30% (41) [69], 64% (52) [70].
Ductal Ca in situ (DCIS)	100% (669) [71], 100% (205) [72], 100% (1106) [73], 100% (467) [21].
Lobular Ca in situ (LCIS)	100% (53) [46], 100% (81) [74], 100% (37) [75], 100% (43) [76].
Paget Disease	62.1% (52) [77], 81.2% (29) [78], 91.2% (148) [79], 84% (104) [80], 60.5% (34) [81], 69% (31) [82], 68% (60) [83].
Male Breast Cancer (MBC)	81.2% (71) [84], 65% (397) [85], 67% (41) [86], 75.3% (42) [87], 77% (87) [88], 70.5% (45) [89], 72.4% (72) [90], 46.4% (69) [87], 68.1% (97) [91], 79.2% (95) [92], 69% (52) [93].
Secretory ca (SC)	87.2% (83) [94]
Lipid-rich ca (LRC)	33.2% (49) [95]
Glycogen-rich clear cell ca	75% (20) [96]

Supplementary Table 2. 5Y-OS of different histological grades of NST breast cancer

Author	G1 (Cases)	G2 (Cases)	G3 (Cases)
Chen ST [97]	88% (59)	73% (720)	65% (355)
Aleskandarany MA [98]	89% (275)	84% (506)	73% (764)
Pinto AE [99]	86% (163)	80% (356)	71% (165)
Xu J [100]	80.8% (26)	57.1% (42)	44.4% (18)
Zhang T [101]	81.9% (72)	63.4% (216)	49.5% (188)
Zhong W [102]	84.8% (105)	60.5% (281)	32.2% (202)
Shi H [103]	84.2% (32)	70.2% (80)	51.9% (54)
Rakha EA [104]	93% (404)	78% (621)	55% (791)

Supplementary Table 3. 5Y-OS of different TNM stages of breast cancer

Author	Cases	0	I	II	III	IV
Dubois JB [105]	392	NA	86.5% (231)	82% (161)	NA	NA
Navarro [106]	3066	NA	90% (1272)	69.5% (1450)	44.6% (242)	20.6% (102)
Migdady Y [107]	161	NA	93.2% (161)	NA	NA	NA
Garassino I [108]	214	NA	96% (214)	NA	NA	NA
Schwartz GF [109]	127	NA	NA	88% (127)	NA	NA
Carey LA [110]	577	95% (86)	84% (71)	72% (121)	47% (299)	NA
Wasif N [111]	235769	NA	94% (123071)	79% (99023)	61% (13675)	NA
Wasif N [111]	27639	NA	95% (12410)	87% (12603)	77% (2626)	NA
Aphinives P [112]	382	NA	100% (9)	85% (214)	39% (130)	9% (29)
Yang MT [113]	263	NA	96.8% (97)	73.7% (102)	46.4% (64)	NA
Zhang P [114]	134	NA	NA	NA	NA	30.1% (134)
Dawood S [115]	643	NA	NA	NA	NA	44% (643)
Bai B [116]	89	NA	NA	NA	NA	4% (89)

NA: No data available.

Supplementary Table 4. 5Y-OS of different molecular types of breast cancer

Author	Luminal-A-like (cases)	Luminal-B-like (cases)	HER2-type (case)	TNBC-type (case)
Lim ST [117] (NST)	88.2% (8196)	84.3% (1638)	73.8% (1528)	68.3% (3185)
Lim ST [117] (ILC)	87% (439)	76% (25)	71.4% (7)	66.7% (57)
Liu ZY [118]	95.56% (145)	84.62% (49)	72.73% (37)	78.57% (53)
García FA [119]	94.2% (840)	83.3% (117)	78.6% (58)	83.3% (152)
Kim J [120]	99.7% (619)	97.7% (96)	91% (117)	92.4% (142)
Kim J [120]	96.5% (1093)	94.5% (212)	92.1% (279)	89.5% (429)
Fan Y [121]	NA	NA	73.1% (111)	NA
Zhang HM [122]	89.83% (248)	86.15% (32)	86.70% (51)	79.85% (77)
Lim SK [123]	86% (167)	85% (65)	85% (35)	59% (55)
Sanpaolo P [124]	93.4% (361)	84.7% (124)	71.9% (134)	71.7% (155)
Bennis S [125]	88% (196)	77% (60)	75% (46)	49% (46)
Xue C [126]	93.3% (1805)	86.6% (760)	77.5% (522)	85.5% (957)
Vallejos CS [127]	81.9%(591)	72.8% (158)	62.4% (194)	67.1% (255)
Zaha DC [128]	86% (92)	75% (33)	60% (5)	60% (38)
Dookeran KA [129]	72% (135)	66.7% (26)	57.0% (25)	53.2% (71)
Guan Y [130]	NA	NA	NA	76.9% (108)
Zhang P [131]	NA	NA	NA	72.9% (94)

NA: No data available.