Clinical significance of exosomes as potential biomarkers in cancer

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Author contributions: Chen YC and Wong CH wrote the paper.

Conflict-of-interest statement: All the authors declare that they have no competing interests.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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Manuscript source: Invited manuscript

Received: October 25, 2018
Peer-review started: October 25, 2018
First decision: November 28, 2018
Revised: December 27, 2018
Accepted: January 3, 2019
Article in press: January 3, 2019
Published online: January 26, 2019

Abstract

BACKGROUND
Exosomes are microvesicles, measuring 30-100 nm in diameter. They are widely distributed in body fluids, including blood, bile, urine and saliva. Cancer-derived exosomes carry a wide variety of DNA, RNA, proteins and lipids, and may serve as novel biomarkers in cancer.

AIM
To summarize the performance of exosomal biomarkers in cancer diagnosis and prognosis.

METHODS
Relevant publications in the literature were identified by search of the “PubMed” database up to September 11, 2018. The quality of the included studies was assessed by QUADAS-2 and REMARK. For assessment of diagnostic biomarkers, 47 biomarkers and 2240 patients from 30 studies were included. For assessment of prognostic markers, 50 biomarkers and 4797 patients from 42 studies were included.

RESULTS
Our results suggested that these exosomal biomarkers had excellent diagnostic ability in various types of cancer, with good sensitivity and specificity. For assessment of prognostic markers, 50 biomarkers and 4797 patients from 42 studies were included. We observed that exosomal biomarkers had prognostic values in overall survival, disease-free survival and recurrence-free survival.

CONCLUSION
Exosomes can function as potential biomarkers in cancer diagnosis and prognosis.

Key words: Exosome; Biomarker; Cancer; Diagnosis; Prognosis
**Core tip:** Cancer-derived exosomes carry a wide variety of DNA, RNA, proteins and lipids, which may serve as novel biomarkers in cancer. The current systematic review and meta-analysis summarized the performance of exosomal biomarkers in cancer diagnosis and prognosis. We analyzed 47 diagnostic markers and 50 prognostic markers from 56 studies with various type of cancer. We found that exosomal biomarkers had both diagnostic and prognostic power in many cancers.

**Citation:** Wong CH, Chen YC. Clinical significance of exosomes as potential biomarkers in cancer. *World J Clin Cases* 2019; 7(2): 171-190

**URL:** https://www.wjgnet.com/2307-8960/full/v7/i2/171.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v7.i2.171

**INTRODUCTION**

Cancer is the uncontrolled growth of cells and eventually leads to death. Cancer is the second cause of death, contributing to more than 8.8 million deaths every year[1,2]. Among various types of cancer, lung cancer, gastrointestinal cancers (GI cancer), including liver cancer, pancreatic cancer and colorectal cancer, and breast cancer are the most common cause of cancer-related death[3-4]. Although chemotherapy, targeted therapy, surgical recession and radiotherapy can effectively prolong survival of patients, the survival rate of cancer is still very low, especially in GI cancer, being less than 20%[5]. One of the major reasons is the late diagnosis of cancer, in which patients are already with advanced and metastatic tumors. As a result, no therapies can effectively kill the cancer cells. The situation is even worse in pancreatic cancers at distant stage, with 5-year survival rate of only 3%[6].

Since more than half of the patients present with locally advanced or metastatic stage, early diagnosis and early treatment are fundamentally important for better prognosis. Therefore, many tumor makers have been developed, aiming at accurately detecting various types of cancer and monitoring the disease progression. Blood test of the tumor antigens carcinoembryonic antigen, carbohydrate antigen 19-9, and carbohydrate antigen 125 (known as CEA, CA19-9 and CA125 respectively) are commonly used for detection of many cancers, such as GI cancers, ovarian cancer and breast cancer[5-8]. However, the sensitivity of these cancer biomarkers is unsatisfactory[9-12]. Also, the fecal occult blood test of colorectal cancer and the invasion endoscopic detection of gastric and colon cancer represent a great inconvenience to the patients. Therefore, highly sensitive and non-invasive diagnostic markers are urgently needed for early detection of cancer.

Exosomes are microvesicles of 30-100 nm diameter, which are secreted by both normal cells and cancer cells. They are distributed in many body fluids such as blood, saliva and urine, and carry various types of biomolecules, including RNA, proteins and lipids, for inter-cellular communication[13-15]. During cancer development, cancer cells secrete more exosomes, with significant changes in composition[16-18]. These facilitate communication within the tumor environment, acquisition of drug resistance, and metastasis to distant organs[19-21]. Although many potential non-invasive biomarkers have been developed using liquid biopsy, such as serum and urine, studies have found that these biomarkers are commonly located in the exosomes[22-23]. Enriching these exosomal biomarkers could achieve a higher diagnostic and prognostic efficiency[24-25]. Thus, exosomal biomarkers can be novel targets in cancer diagnosis and prognosis.

The objective of this systemic review and meta-analysis is to evaluate the diagnostic and prognostic potential of exosomes in patients with various types of cancer, based on current available data. This information will help in the development of novel non-invasive biomarkers for sensitive and specific diagnosis and prognosis of cancer.

**MATERIALS AND METHODS**

**Search strategy**

Electronic literature search was performed using the PubMed database, without any language restriction. Articles related to exosomes in cancer from 2010 to September 11, 2018 were identified using the following key words: “exosome” and “cancer” and...
“diagnosis” or “prognosis”.

Inclusion and exclusion criteria
Articles were reviewed by their titles, key words, abstracts and full text to identify eligible studies. Eligible studies were included based on the following inclusion criteria: (1) The original article was related to exosomal diagnostic or prognostic markers in cancer; (2) At least 10 patients and 10 matched controls were enrolled in the study; (3) For diagnostic markers, enough information, such as specificity and sensitivity, was provided to construct a 2 × 2 table [true positive (TP), true negative (TN), false positive (FP), false negative (FN)]; and (4) For prognostic markers, enough information was provided to estimate the hazard ratios (HRs) and confidence intervals (CIs). The exclusion criteria were as follows: (1) Duplicate articles; (2) Review articles, abstracts, comments, letters, case-report; (3) Fundamental research or animal study; (4) Diagnostic or prognostic marker that was not specific to exosome; (5) Sample size was less than 10; (6) Performance of the biomarker was not statistically significant; or (7) Incomplete information to estimate diagnostic or prognostic accuracy.

Data extraction
Two reviewers (Chi-Hin Wong and Yang-Chao Chen) independently reviewed and extracted the data from the eligible studies according to the listed criteria. Any disagreement was resolved by consensus among the authors. The following data from included studies were extracted: first author’s name, year of publication, sample size, cancer type, country of origin, source of exosome, isolation method of exosome, and detection method of biomarkers. For diagnostic studies, data for the cut-off value of tested targets, sensitivity, specificity, and area under the receiver operating characteristics curve (ROC) were also extracted. For prognostic studies, data for survival analysis, cut-off value, multivariable HR and its 95%CI were extracted. If OR was reported, OR was converted to relative risk using the formula introduced by Zhang and Yu[27]. If either OR or HR was not reported, the method introduced by Tierney et al[28] was used to estimate the HR and its 95%CI from a Kaplan-Meier plot.

Quality assessment
For diagnostic studies, the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) was used to assess the quality of studies for the meta-analysis[29]. Briefly, 14 questions covering the patient selection, patient flow, index test and reference standard test were applied to each study and an answer of “Yes”, “No” or “Unclear” was given to each study. Only answers of “Yes” were given a score. For prognostic study, the quality of studies was assessed according to reporting recommendations for tumor marker prognostic studies (REMARK)[30]. Briefly, a checklist of 20 items was generated, covering patients’ characteristics, samples’ source and storage, assay methods, statistical analysis, and data interpretation. A score was given when the study fulfilled the requirement of each item.

Statistical analysis
The statistical analysis of the diagnostic performance of biomarkers was performed using Meta-DiSc 1.4[31]. The 2 × 2 table of each study was used to assess the pooled sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR). Also, the summary receiver operating characteristic (SROC) curve was plotted; the area under the curve (AUC) was calculated and Q* index was estimated to assess the overall performance in cancer diagnosis. An AUC of 0.5 suggested no diagnostic ability; 0.7-0.8 suggested acceptable diagnostic performance; 0.8-0.9 was considered excellent, and 0.9-1.0 suggested outstanding performance[32]. Q* was defined at a point in which sensitivity and specificity are equal. For statistical analysis of the prognostic performance of biomarkers, forest plots were constructed using the HR and its 95%CI of each biomarker to assess the overall prognostic performance of biomarkers on overall survival (OS), disease-free survival (DFS) and recurrence-free survival (RFS). Graphpad Prism 6 was used in constructing the forest plots. To elevate the heterogeneity between studies, Cochran-Q test and inconsistency index (I²) statistics were calculated[33,34]. P-value of < 0.05 for Cochran-Q test or I² >50% suggested the presence of heterogeneity.

RESULTS

Literature search
Initially, 1233 articles were identified based on the search strategies. Based on title and
Abstract biomarkers could effectively discriminate cancer patients from healthy people respectively (Figure 7). The high sensitivity, specificity and Q* demonstrated that the pooled biomarkers also had a good sensitivity of 0.77 and specificity of 0.79 in detecting prostate cancer (4 studies with 7 biomarkers (Figures 3-7). We observed that the diagnostic OR was 20.35 (Figure 3E). Importantly, many studies did not provide enough information on how the patients were selected and classified. Patients excluded from the 2 × 2 table were often observed in some studies.

The REMARK system was used to assess the quality of prognostic studies (Figure 2B). Most of the studies (> 90%) clearly stated the objective, biomarkers examined, source of exosomes, and methodology of isolation and detection. Also, most of the studies clearly defined the clinical endpoints and the period of the follow-up time. However, details in patient’s characteristics during the follow-up period, such as the use of post-operative adjuvant therapy which significantly affects the OS and DFS, were lacking in most of the studies. Important, some studies did not clearly report the clinicopathological characteristics of the patients enrolled. Also, some studies did not show the relationship of the tested biomarkers to prognostic variables, including tumor stages and tumor differentiation. Twelve prognostic marker studies did not perform univariable or multivariable analysis. Twenty-eight of the enrolled studies reported multivariable analysis in prognostic markers, but only five studies clearly stated the adjustment factors.

Diagnostic markers
Diagnostic markers from 30 studies were included in the meta-analysis (Table 1). More than a half of these studies were related to GI cancers (4 studies were about colon cancer; 5 studies were related to liver cancer; 4 studies were about pancreatic or pancreatobiliary tract cancer; and 4 studies were related to gastric cancer). A total of 2240 patients were included in the meta-analysis, with 12 studies having enrolled < 50 patients, 16 studies having enrolled 50-100 patients, and 6 studies having enrolled > 100 patients. There were 47 diagnostic biomarkers analyzed in the meta-analysis. There were 42.6% of the biomarkers as miRNAs, followed by lncRNAs (36.2%) and proteins (19.1%). Notably, 6 studies analyzed the diagnostic performance of exosomal miR-21 in various types of cancer. Also, 61.3%, 16.1%, 12.9%, 3.2% and 3.2% of the biomarkers were detected in serum, plasma, urine, saliva and bile respectively.

Since a wide range of cancers was studied by different groups, we separated the diagnostic biomarkers according to cancer types and meta-analyzed cancer types with more than three biomarkers studied. Therefore, we focused on colorectal cancer (4 studies with 11 biomarkers), gastric cancer (4 studies with 5 biomarkers), pancreatic cancer (4 studies with 8 biomarkers), liver cancer (4 studies with 7 biomarkers), and prostate cancer (4 studies with 7 biomarkers (Figures 3-7). We observed that the pooled biomarkers had a good specificity of 0.87 but poor sensitivity of 0.57 in colorectal cancer diagnosis (Figure 3A and B). The PLR and NLR were 2.02 and 0.21 respectively (Figure 3C and D). The diagnostic OR was 20.35 (Figure 3E). Importantly, the AUC of the SROC curve was 0.89 and the Q* was 0.82 (Figure 3F). In diagnosis of gastric cancer, we observed that the pooled biomarkers had a good sensitivity of 0.77 and specificity of 0.73 with PLR, NLR, AUC of the SROC curve and Q* of 2.94, 0.32, 9.88, 0.84 and 0.77 respectively (Figure 4). For diagnosis of pancreatic cancer, we also observed the pooled biomarkers had an excellent sensitivity of 0.91 and specificity of 0.90 with PLR, NLR, AUC of the SROC curve and Q* of 6.35, 0.19, 40.71, 0.94 and 0.88 respectively (Figure 5). In liver cancer, the pooled biomarkers had a good diagnostic sensitivity of 0.76 and specificity of 0.80 with PLR, NLR, AUC of the SROC curve and Q* of 3.51, 0.32, 12.45, 0.85 and 0.78 respectively (Figure 6). The pooled biomarkers also had a good sensitivity of 0.77 and specificity of 0.79 in detecting prostate cancer with PLR, NLR, AUC of the SROC curve and Q* of 3.84, 0.28, 17.88, 0.88 and 0.80 respectively (Figure 7). The high sensitivity, specificity and Q* demonstrated that the pooled biomarkers could effectively discriminate cancer patients from healthy people or non-cancer patients.
Figure 1 Literature search process to select studies which evaluated the diagnostic or prognostic performance of exosomal biomarkers in cancer.

Prognostic markers
Prognostic biomarkers from 42 studies were included in the systematic review (Table 2). In total, 4797 patients were represented among the studies, with 7 studies having enrolled < 50 patients, 15 studies having enrolled 50-100 patients, and 20 studies having enrolled > 100 patients. There were 50 prognostic biomarkers analyzed in the systematic review, with 60% of the biomarkers being miRNAs, followed by lncRNAs (18%) and proteins (16%). Also, 50%, 43%, 2.4%, 2.4% and 2.4% of the biomarkers were detected in serum, plasma, bile, ascetic fluid and cell-free effusion supernatant respectively. For the included studies, 92.9%, 26.2% and 9.5% used OS, DFS and RFS respectively as the primary endpoints. In addition, a wide range of cancers was studied by the different groups. More than one-half of the included studies were related to GI cancers (11 studies were about colorectal or colon cancer, 5 studies were related to liver cancer, 5 studies were about pancreatic cancer, and 4 studies were related to gastric cancer). In this meta-analysis, we separated studies according to clinical endpoints and focused on cancer types with more than three biomarkers studied.

For 13 biomarkers with OS reported in colon cancer, the pooled HR was 1.833 with I$^2$ of 62.14% and $P = 0.002$ (Figure 8A). Also, for 5 biomarkers with DFS reported in colon cancer, the pooled HR was 3.035 with I$^2$ of 0.00% and $P = 0.536$ (Figure 8B). Furthermore, for 4 biomarkers with RFS reported in colon cancer, the pooled HR was 1.645 with I$^2$ of 89.61% and $P = 0.000$ (Figure 8C). Apart from colon cancer, for the 4 biomarkers with OS reported in gastric cancer, the pooled HR was 1.836 with I$^2$ of 96.71 and $P = 0.000$ (Figure 9). In addition, for the 4 biomarkers with OS reported in pancreatic cancer, the pooled HR was 1.537 with I$^2$ of 81.50 and $P = 0.001$ (Figure 10). For 5 biomarkers, the pooled HR was 1.828, I$^2$ of 84.48% and $P = 0.000$ for prognosing OS in liver cancer (Figure 11). Also, 9 biomarkers with the pooled HR of 0.895, I$^2$ of 89.50% and $P = 0.000$ were reported to function as prognostic biomarkers of OS in lung cancer (Figure 12). These results demonstrated that exosomes were associated with OS, DFS and RFS in various types of cancer.

DISCUSSION
Exosomes play important roles in cancer development via intercellular communication, promoting cell metastasis and developing drug resistance[19-21]. Importantly, exosomes are frequently secreted by the cancers and are widely distributed in many body fluids. Therefore, they can be detected in blood, saliva and urine. Exosomal biomarkers have better performance in cancer diagnosis and prognosis than liquid biopsy used alone[24-26]. However, the methods of isolating exosomes from liquid biopsy varies between studies. Ultracentrifugation or the use of commercial isolation kits are common methods in extracting exosomes. Ultracentrifugation gives highly pure exosomes but the isolation efficiency is relatively low; whereas, the use of commercial kits maximizes the efficiency with the
loss of purity\(^\textsuperscript{[95,96]}\). Therefore, a standardized protocol of detecting exosomal biomarkers is greatly needed.

There are some limitations of our meta-analysis. We excluded studies that utilized combined biomarkers because this cannot tell the performance of individual biomarkers\(^\textsuperscript{[97,98]}\). For example, a six-microRNA panel was developed for diagnosis of lung cancer but miR-409-3p, miR-425-5p and miR-584-5p were not significantly dysregulated in patients’ exosomes\(^\textsuperscript{[98]}\). This may reduce the diagnostic performance of other biomarkers in the same panel. Since many of the individual biomarkers in the panel were significantly differentially expressed in cancer exosomes, further studies may be needed to explore the correlation of these potential biomarkers with patients’ characteristics and their performances in cancer diagnosis and prognosis.

A further limitation is that we focused on exosomal markers only in cancer diagnosis and prognosis and excluded tissue-based biomarkers from this meta-analysis. In fact, many studies have reported that expression levels in exosomes and in tissues are highly associated\(^\textsuperscript{[35,66]}\). This suggests that many exosomal markers can reflect the situation in cancer cells, and this notion has been developed for potential biomarkers in various cancers. Importantly, this strong association may also suggest that many tissue-based biomarkers can be developed into non-invasive exosomal biomarkers in cancer diagnosis.

Notably, most of the included studies are retrospective, having been performed on stored samples. However, the main disadvantage of the retrospective study is its lack of complete clinicopathological information\(^\textsuperscript{[30]}\), which lowers the quality of study. Despite the above limitations, our meta-analysis indicates that exosomes can be potential biomarkers in cancer diagnosis and prognosis. Further large prospective studies are greatly needed to clarify the performance of exosomal biomarkers in cancer diagnosis and prognosis.
| Ref.                  | Country | Cancer type | Stage          | Control Type | Num of Control | Num of patients | Sample Type | Isolation method of exosome | Marker | Detection method | Cut-off | TP | TN | FP | FN |
|----------------------|---------|-------------|----------------|---------------|----------------|----------------|-------------|----------------------------|--------|-----------------|---------|----|----|----|----|
| Sun et al [39]       | China   | Colorectal  | All            | Healthy       | 32             | 92             | Plasma      | UC                         | CPNE3  | ELISA           | 0.143   | 62 | 27 | 5  | 30 |
| Ogata-Kawata et al [34] | Japan   | Colorectal  | All            | Healthy       | 11             | 88             | Serum       | UC                         | miR-1246 | qRT-PCR         | 1.45    | 84 | 10 | 4  | 1  |
| Liu et al [37]       | China   | Colorectal  | All            | Healthy and benign | 320            | 148            | Serum       | ExoQuick                  | CRNDE-h | qRT-PCR         | 0.02    | 104 | 302 | 18 | 44 |
| Uratani et al [38]   | Japan   | Colorectal  | All            | Healthy       | 47             | 26             | Serum       | ExoQuick                  | miR-21  | qRT-PCR         | Youden index | 18 | 38 | 9  | 8  |
| Lin et al [40]       | China   | Gastric     | All            | Healthy       | 60             | 51             | Plasma      | UC                         | IncUEG C1 | qRT-PCR         | NR      | 45 | 50 | 10 | 6  |
| Zhao et al [41]      | China   | Gastric     | All            | Healthy       | 120            | 126            | Serum       | NR                         | HOTTIP  | qRT-PCR         | 1.72    | 88 | 102 | 18 | 38 |
| Pang et al [42]      | China   | Gastric     | All            | Healthy       | 37             | 40             | Serum       | ExoQuick                  | ZFAS1   | qRT-PCR         | NR      | 32 | 28 | 9  | 8  |
| Yang et al [43]      | China   | Gastric     | All            | Healthy       | 80             | 80             | Serum       | ExoQuick                  | miR-423-5p | qRT-PCR         | NR      | 65 | 46 | 34 | 15 |
| Goto et al [45]      | Japan   | Pancreatic   | All            | Healthy and advanced pancreatic cancer | 22             | 23             | Serum       | ExoQuick                  | miR-191 | qRT-PCR         | Distanc e = (1- sensitivit y2) * (1- specificit y2) in ROC curve | 18 | 17 | 5  | 5  |
| Melo et al [46]      | German y | Pancreatic   | All            | Healthy       | 100            | 190            | Serum       | UC                         | GPC1    | Flow cytometry  | Youden index | 190 | 100 | 0  | 0  |
| Que et al [47]       | China   | Pancreatic   | All            | Non-PDAC      | 27             | 22             | Serum       | UC                         | miR-17-5p | qRT-PCR         | 6.826   | 20 | 20 | 7  | 2  |
| Machida et al [48]   | Japan   | Pancreatic   | II-IV          | Healthy       | 13             | 12             | Saliva      | Total exosome isolation kit | miR-21 | qRT-PCR         | 7.693   | 18 | 26 | 1  | 4  |
| Xu et al [49]        | China   | Liver        | All            | Chronic hepatitis B | 68             | 88             | Serum       | Total exosome isolation kit | hnRNP H1 | qRT-PCR         | 13.77   | 8  | 13 | 0  | 4  |
|                       |         |             |                |               |                |                |            |                            |         |                | 5.205   | 9  | 10 | 3  | 3  |
|                       |         |             |                |               |                |                |            |                            | 0.67    | 75 | 52 | 16 | 13 |
| Authors | Country | Tissue | Stage/Type | Sample Size | Exosome Source | miRNA | PCR Method | Result | R U  |
|---------|---------|--------|------------|-------------|----------------|--------|-------------|--------|------|
| San et al. | China | Liver | All Healthy | 56 56 | Serum | Total extracellular exosome iso | LINCO0161 | NR | 42 | 41 | 15 | 14 |
| Xu et al. | China | Liver | All Chronic hepatitis B | 96 60 | Serum | Total extracellular exosome iso | ENSGO0002583-32.1 | 1.345 | 43 | 80 | 16 | 17 |
| | | | | 60 55 | | | ENSGO0002583-32.1 | 1.366 | 40 | 48 | 12 | 15 |
| | | | | 96 60 | | | LINCO0635 | 1.69 | 46 | 75 | 21 | 14 |
| | | | | 60 55 | | | LINCO0635 | 1.532 | 44 | 45 | 15 | 11 |
| Goldyasser et al. | Israel | Pan-cancer (not include liver) | Healthy | 45 98 | Serum | Total extracellular exosome iso | hTERT | NR | 61 | 45 | 0 | 37 |
| Zhang et al. | China | Lung | All Healthy | 45 35 | Serum | | ExoQuick | MALAT-1 | NR | 21 | 45 | 0 | 14 |
| | | | | 30 77 | | | UC 14-3-3ζ | NR | 62 | 21 | 9 | 15 |
| | | | | 15 15 | Plasma | UC | | ELISA | 9 | 12 | 3 | 6 |
| Li et al. | NR | Ovarian | Benign | 21 50 | Serum | | ephrinA2 | ELISA | 20.4 | ng/L | 44 | 17 | 4 | 6 |
| Meng et al. | NR | Ovarian | All Benign | 20 163 | Serum | Total extracellular exosome iso | miR-20a | PCR+ | Youden index | 135 | 18 | 2 | 28 |
| | | | | | | miR-20b | qRT-PCR | | | 86 | 20 | 0 | 77 |
| | | | | | | miR-100 | | | | 51 | 20 | 0 | 112 |
| Pan et al. | German | Ovarian | Healthy | 29 106 | Plasma | | ExoQuick | MALAT-1 | NR | 21 | 45 | 0 | 14 |
| | | | | | | MALAT-1 | NR | 62 | 21 | 9 | 15 |
| | | | | | | UC 14-3-3ζ | ELISA | 9 | 12 | 3 | 6 |
| Bryzgunova et al. | Russia | Prostate | All Healthy | 20 14 | Urine | | UC | | | 12 | 13 | 7 | 2 |
| Wang et al. | China | Prostate | II-IV Healthy | 30 34 | Plasma | Total extracellular exosome iso | SAP30L-AS1 | qRT-PCR | Youden index | 65 | 24 | 5 | 41 |
| | | | | | | SCHLAP1 | | | 66 | 21 | 8 | 40 |
| | | | | | | | | | 68 | 25 | 4 | 38 |
| | | | | | | | | | 59 | 20 | 9 | 47 |
| Øverbøye et al. | NR | Prostate | All Healthy | 15 16 | Urine | | UC | | | 12 | 16 | 0 | 3 |
| | | | | | | | | | 14 | 16 | 0 | 1 |
| Işın et al. | NR | Prostate | All BPH | 49 30 | Urine | Urine extracellular exosome RNA isolation kit | LincRNA-p21 | qRT-PCR | Youden index | 0.181 | 20 | 31 | 18 | 10 |
| Wang et al. | China | Laryngeal | All Vocal cord polyps | 49 52 | Serum | | ExoQuick | malTAIR | qRT-PCR | 0.043 | 36 | 40 | 9 | 16 |
| | | | | | | | HOTAIR | | | 0.032 | 48 | 28 | 21 | 4 |
| Alegre et al. | NR | Melanoma | NR Healthy | 25 53 | Serum | | ExoQuick | exosomal | ELISA | 1.4 | μg/L | 42 | 20 | 5 | 11 |
| | | | | | | | RNA | ELISA | 0.015 | μg/L | 42 | 20 | 5 | 11 |
| Manterola et al. | France | GBM | NR Healthy | 30 50 | Serum | | ExoQuick | RNU6E | qRT-PCR | 0.372 | 33 | 20 | 10 | 17 |
| Chen et al. | Taiwan | Bladder | All hernia | 81 140 | Urine | | UC | TACPST | ELISA | 2.47 | ng/mL | 103 | 62 | 19 | 37 |
UC: Ultracentrifugation; NR: Not reported.

### Table 2  Studies included for meta-analysis of exosomal biomarkers in cancer prognosis

| Ref.          | Period       | Country     | Sample Size | Cancer Type | Stage | Sample | Isolation method of exosome | Marker | Detection method | Cut-off value | Survival analysis | HR (95%CI) |
|---------------|--------------|-------------|-------------|-------------|-------|--------|--------------------------------|--------|-------------------|--------------|-------------------|------------|
| Peng et al[c] | 2008-2014    | China       | 108         | Colorectal  | All   | Serum  | Total exosome isolation kit  | miR-548c-5p | qRT-PCR           | NR           | OS                | 3.40 (1.02-11.27) |
| Sun et al[c]  | 2012-2017    | China       | 92          | Colorectal  | All   | Plasma | UC CPNE3                         | ≥ 0.143 PR/PR exosome | ELISA            | OS           | DFS              | 3.0 (1.0-8.9)   |
| Tsukamoto et al[c] | 2002-2012 | Japan       | 326         | Colorectal  | II-IV | Plasma | UC miR-21                        | qRT-PCR | ≥ median        | OS           | DFS              | 2.28 (1.81-5.74) |
| Liu et al[c]  | 2007-2010    | China       | 148         | Colorectal  | All   | Serum  | ExoQuick CRNDE-h                | miR-4772-3p | qRT-PCR           | > 0.02        | OS                | 2.00 (1.269-3.154) |
| Liu et al[c]  | 2006-2011    | United States | 84         | Colorectal  | II-III| Serum  | ExoQuick                         | miR-21 | qRT-PCR           | ≥ 27.88       | OS                | 6.19 (1.50-25.5) |
| Liu et al[c]  | 2013-2014    | China       | 158         | Colorectal  | All   | Plasma | UC lncRNA GASS                  | qRT-PCR | ≥ median        | OS           | DFS              | 5.48 (2.49-12.1) |
| Gao et al[c]  | 2011-2014    | China       | 108         | Colorectal  | All   | Serum  | ExoQuick                         | 91H     | qRT-PCR           | ≥ 0.85        | RFS               | 7.14 (1.23-21.35) |
| Yan et al[c]  | NR           | NR          | 168         | Colorectal  | All   | Serum  | Total Exosome Isolation kit     | miR-6803 | qRT-PCR           | NR           | OS                | 2.93 (1.35-6.37) |
| Li et al[c]   | 2013-2015    | China       | 85          | Colorectal  | III   | Plasma | ExoCapTM GPC1                   | Flow cytometry | > mean | OS           | 1.89 (1.23-2.89) |
| Silva et al[c] | 2003-2009 | Spain       | 91          | Colorectal  | All   | Plasma | UC Exosome                       | Flow cytometry of EpCAM | High    | OS           | 0.87 (0.57-1.32) |
| Matsumura et al[c] | 1992-2007 | Japan       | 209         | Colorectal  | All   | Serum  | UC miR-19                        | qRT-PCR | > mean        | O            | DFS              | 2.49 (1.12-6.61) |
| Yan et al[c]  | 2012-2015    | China       | 142         | Colorectal  | All   | Serum  | Total Exosome Isolation kit     | miR-6869-5p | qRT-PCR           | < mean       | OS                | 2.32 (1.08-4.99) |

[1] Biliary obstruction
| Authors          | Year  | Country | Type      | Tissue | Fluid     | Methods                  | Target(s)                  | p-Value       | Stage | Follow-up | N | OS          | Hazard Ratio | CI          | DFS          |
|------------------|-------|---------|-----------|--------|-----------|--------------------------|----------------------------|---------------|-------|-----------|----|-------------|--------------|------------|--------------|
| Santaus and al   | 2009-2013 | Spain   | Colon    | I-III  | Plasma    | UC, miR-141, qRT-PCR     | High                       | 1.89 (0.93-3.83) |       |           |    |             |              |            |              |
| Zhao et al       | 2011-2012 | China   | Gastric  | All    | Serum     | HOTTIP, qRT-PCR          | > 1.72                     | OS            | 2.037 (1.085-3.823) |       |           |    |             |              |            |              |
| Liu et al        | 2012-2017 | China   | Gastric  | All    | Serum     | Total Exosome Isolation kit, miR-451, qRT-PCR | > median, 5yr-OS | 4.344 (2.685-5.721) |       |           |    |             |              |            |              |
| Yang et al       | NR    | China   | Gastric  | All    | Serum     | ExoQuick, miR-423-5p, qRT-PCR | > median                | DFS           | 1.93 (1.25-2.99) |       |           |    |             |              |            |              |
| Kumata et al     | 2006-2013 | Japan   | Gastric  | All    | Plasma    | UC, miR23b, qRT-PCR      | > 0.78                    | OS            | 0.57 (0.370-0.78) |       |           |    |             |              |            |              |
| Zhou et al       | 2010-2014 | China   | Pancreatic | All    | Plasma    | ExoQuick, miR-125b-5p, qRT-PCR | < median               | OS            | 0.285 (0.108-0.75) |       |           |    |             |              |            |              |
| Li et al         | 2012-2016 | China   | Pancreatic | All    | Plasma    | circPDE8A, qRT-PCR      | > median                | OS            | 1.764 (1.064-2.925) |       |           |    |             |              |            |              |
| Goto et al       | 2013-2015 | Japan   | Pancreatic | All    | Serum     | ExoQuick, miR-21, qRT-PCR | > median                | OS            | 4.071 (1.832-9.996) |       |           |    |             |              |            |              |
| Takahashi et al  | 2013-2017 | Japan   | Pancreatic | I-II   | Plasma    | UC, miR-451a, qRT-PCR    | < 1.75                   | OS            | 3.20 (1.07-11.94) |       |           |    |             |              |            |              |
| Xu et al         | 2012-2016 | China   | Liver    | All    | Serum     | Total Exosome Isolation kit, ENSG00000258332.1 LINC00635, miR-638, qRT-PCR | > 1.845 | OS            | 2.22 (1.34-3.68) |       |           |    |             |              |            |              |
| Shi et al        | 2008-2011 | China   | Liver    | All    | Serum     | Total Exosome Isolation kit, miR-638, qRT-PCR | NR, 3yr-OS | 3.52 (1.37-6.02) |       |           |    |             |              |            |              |
| Liu et al        | 2012    | China   | Liver    | All    | Serum     | ExoQuick, miR-125b, qRT-PCR | < median                | RFS          | 0.14 (0.07-0.29) |       |           |    |             |              |            |              |
| Xue et al        | 2015-2017 | China   | Liver    | All    | Serum     | Total Exosome Isolation kit, miR-93, qRT-PCR | NR, OS               | 1.47 (0.96-2.25) |       |           |    |             |              |            |              |
| Liu et al        | 2008-2013 | China   | Hepatoblastoma (children) | All    | Serum     | ExoQuick, miR-21, qRT-PCR | NR, EFS | 1.434 (1.257-2.766) |       |           |    |             |              |            |              |
| Matsumoto et al  | 2011-2012 | Japan   | Esophageal | All    | Plasma    | Total Exosome Isolation kit, exosome AChE activity | < 600 x 108/mL | OS            | 2.177 (1.085-3.605) |       |           |    |             |              |            |              |
| Lu et al         | 2007-2015 | China   | Nasopharyngeal | All    | Plasma    | UC, miR-9, qRT-PCR | NR, OS | 1.5 (1.03-2.18) |       |           |    |             |              |            |              |
| Ye et al         | 2011-2013 | China   | Nasopharyngeal | II-IV  | Serum     | protein concentration BCA assay | > 11 μg/mL | DFS          | 214.22 (139.27-329.49) |       |           |    |             |              |            |              |
| Huang et al      | NR     | NR      | Prostate | All    | Plasma    | ExoQuick, miR-1290, qRT-PCR | > mean | OS            | 1.79 (1.30-2.48) |       |           |    |             |              |            |              |
| Tang et al       | NR     | NR      | Ovarian  | All    | Ascitic fluid | UC, E-cadherin | > 10 μg/mL | OS            | 1.82 (0.53-3.58) |       |           |    |             |              |            |              |
| Vaksman et al    | 1998-2003 | Ovarian | III-IV   | Effusion supernatant | UC, Exosome | miR-21, qRT-PCR | > mean | OS            | 1.70 (1.1-2.59) |       |           |    |             |              |            |              |
| Study                | Years     | Location | Tissue | Method | miRNA | Assay       | Cut-off | OS (95% CI) | DFS (95% CI) |
|---------------------|-----------|----------|--------|--------|-------|-------------|---------|-------------|--------------|
| Kanaoka et al.     | 2012-2017 | Japan    | Lung I-III | Plasma | UC    | miR-451a     | qRT-PCR | > 1.45      | 6.06 (2.61-15.94) |
|                     |           |          |        |        |       |             |         |             | 2.55 (1.44-4.65) |
| Liu et al.         | 2012-2014 | China    | Lung   | All    | Plasma | miR-23b-3p  | qRT-PCR | High        | 2.42 (1.45-4.04)  |
|                     |           |          |        |        |        | miR-21-5p   | qRT-PCR | OS          | 2.12 (1.28-3.49)  |
|                     |           |          |        |        |        | miR-10b-5p  | qRT-PCR | OS          | 2.22 (1.18-4.16)  |
| Liu et al.         | 2012-2014 | China    | Lung   | All    | Plasma | miR-23b-3p  | qRT-PCR | OS          | 2.12 (1.45-4.04)  |
|                     |           |          |        |        |        | miR-21-5p   | qRT-PCR | OS          | 2.12 (1.28-3.49)  |
|                     |           |          |        |        |        | miR-10b-5p  | qRT-PCR | OS          | 2.22 (1.18-4.16)  |
| Sandfeld et al.    | 2011-2014 | Denmark  | Lung   | All    | Plasma | /         | CD171   | Exosome AChE activity | 1.72 (1.05-2.83)  |
|                     |           |          |        |        |        |            |         |             |              |
| Manier et al.      | 2006-2008 | France   | Multiple | All    | Plasma | let-7b     | let-7b  | < median    | 2.83 (1.07-7.50)  |
|                     |           |          | myeloma|        |        |            |         |             | 1.90 (1.22-2.94)  |
|                     |           |          |        |        |        |            |         |             | 2.01 (1.30-3.11)  |
|                     |           |          |        |        |        |            |         |             | 2.34 (1.52-3.61)  |
|                     |           |          |        |        |        |            |         |             | 3.54 (2.21-5.68)  |
|                     |           |          |        |        |        |            |         |             | 2.41 (1.06-6.03)  |
|                     |           |          |        |        |        |            |         |             | 1.76 (1.15-2.69)  |
|                     |           |          |        |        |        |            |         |             | 2.21 (1.41-3.47)  |
|                     |           |          |        |        |        |            |         |             | 2.29 (1.48-3.55)  |
|                     |           |          |        |        |        |            |         |             | 4.52 (1.57-12.98) |
|                     |           |          |        |        |        |            |         |             | 2.76 (1.79-4.26)  |
|                     |           |          |        |        |        |            |         |             | 3.11 (1.52-3.36)  |
| Alegre et al.      | NR        | NR       | 53     | Melanoma | Serum | MIA        | ELISA   | 2.5 μg/L    | 1.28 (0.65-2.51)  |
|                     |           |          |        |        |        |            |         |             | 4.4 (3.1-9.6)      |
| Lan et al.         | 2011-2012 | China    | 60     | Glioma  | All    | miR-301a   | qRT-PCR | > median    | 2.40 (1.24-4.66)  |
|                     |           |          |        |        |        | qRT-PCR    |         | OS          | 1.55 (0.80-3.01)  |
| Ge et al.          | NR        | China    | 35     | Cholangio carcinoma | Bile | ENST0000588480.1 | qRT-PCR | > median    | 9.1 (1.8-166.1)   |
| Fujii et al.       | 2005-2014 | Japan    | 108    | Renal cell | I-III | miR-224    | qRT-PCR | > median    | 9.1 (1.8-166.1)   |

UC: Ultracentrifugation; OS: Overall survival; DFS: Disease-free survival; RFS: Recurrence free survival; EFC: Event-free survival; NR: Not reported.
Figure 3  Forest plot of pooled (A) sensitivity, (B) specificity, (C) positive likelihood ratio, (D) negative likelihood ratio, (E) diagnostic odds ratio and (F) SROC curve of exosomal biomarkers in diagnosis of colon cancer. SROC: Summary receiver operating characteristic.

Figure 4  Forest plot of pooled (A) sensitivity, (B) specificity, (C) positive likelihood ratio, (D) negative likelihood ratio, (E) diagnostic odds ratio, and (F) WJCC
**Figure 5** Forest plot of pooled (A) sensitivity, (B) specificity, (C) positive likelihood ratio, (D) negative likelihood ratio, (E) diagnostic odds ratio and (F) SROC curve of exosomal biomarkers in diagnosis of pancreatic cancer. SROC: Summary receiver operating characteristic.
Figure 6  Forest plot of pooled (A) sensitivity, (B) specificity, (C) positive likelihood ratio, (D) negative likelihood ratio, (E) diagnostic odds ratio, and (F) SROC curve of exosomal biomarkers in diagnosis of liver cancers. SROC: Summary receiver operating characteristic.

Figure 7  Forest plot of pooled (A) sensitivity, (B) specificity, (C) positive likelihood ratio, (D) negative likelihood ratio, (E) diagnostic odds ratio, and (F) SROC curve of exosomal biomarkers in diagnosis of prostate cancers. SROC: Summary receiver operating characteristic.
Figure 8  Forest plot evaluating the effect of exosomal markers on overall survival (A), disease-free survival (B), and (C) recurrence-free survival of patients with colon cancer.

| Model | Study name | Statistics for each study | Hazard ratio and 95%CI |
|-------|------------|---------------------------|------------------------|
|       |            | Hazard ratio | Upper limit | Lower limit | 0.01 | 0.10 | 1.00 | 10.00 | 100.00 |
| Peng miR-548c-5p | 3.400 | 11.304 | 1.023 | |
| Sun CNP63 | 3.000 | 8.950 | 1.606 | |
| Tsukamoto miR-21 | 2.863 | 5.740 | 1.306 | |
| Liu DORR-h | 2.009 | 3.533 | 1.269 | |
| Liu miR-4772-3p | 6.190 | 25.320 | 1.510 | |
| Liu IncRNA GAS5 | 0.265 | 0.855 | 0.083 | |
| Liu miR-221 | 2.141 | 3.054 | 1.501 | |
| Yan miR-8003 | 2.930 | 6.368 | 1.349 | |
| Li GFC1 | 1.960 | 3.930 | 0.233 | |
| Silva Exosoma | 0.870 | 3.124 | 0.572 | |
| Matsumura miR-19 | 2.490 | 6.610 | 0.938 | |
| Yan miR-6869-3p | 1.320 | 4.067 | 1.079 | |
| Sentaussaqui miR-141 | 1.980 | 3.835 | 0.931 | |

Figure 9  Forest plot evaluating the effect of exosomal markers on overall survival of patients with gastric cancer.

| Model | Study name | Statistics for each study | Hazard ratio and 95%CI |
|-------|------------|---------------------------|------------------------|
|       |            | Hazard ratio | Upper limit | Lower limit | 0.01 | 0.10 | 1.00 | 10.00 | 100.00 |
| Sun CNP63 | 2.500 | 5.590 | 1.118 | |
| Tsukamoto miR-21 | 2.340 | 4.680 | 1.130 | |
| Liu miR-4772-3p | 5.480 | 12.090 | 2.486 | |
| Yan miR-8003 | 3.260 | 6.811 | 1.560 | |
| Matsumura miR-19 | 2.490 | 6.610 | 0.938 | |

Figure 10  Forest plot evaluating the effect of exosomal markers on overall survival of patients with pancreatic cancer.

| Model | Study name | Statistics for each study | Hazard ratio and 95%CI |
|-------|------------|---------------------------|------------------------|
|       |            | Hazard ratio | Upper limit | Lower limit | 0.01 | 0.10 | 1.00 | 10.00 | 100.00 |
| Zhao HOTTIP | 2.037 | 3.824 | 1.085 | |
| Liu miR-451 | 4.344 | 5.721 | 3.298 | |
| Yang miR-433-5p | 1.930 | 2.985 | 1.248 | |
| Kurnata miR-23b | 0.570 | 0.780 | 0.417 | |

Wong CH et al. Clinical significance of exosomes

WJCC  | https://www.wjgnet.com
January 26, 2019  | Volume 7  | Issue 2  | 185
ARTICLE HIGHLIGHTS

Research background
Exosomes, which are widely distributed in body fluids, including blood, bile, urine and saliva, are microvesicles of 30-100 nm diameter in size. Cancer-derived exosomes carry a wide variety of DNA, RNA, proteins and lipids, and may serve as novel biomarkers in cancer.

Research motivation
Exosomes may function as exosomal biomarkers in cancer diagnosis and prognosis.

Research objectives
To summarize the performance of exosomal biomarkers in cancer diagnosis and prognosis.

Research methods
Relevant studies in the literature were identified using the PubMed database. QUADAS-2 and REMARK were used to assess the quality of the included studies. For diagnostic biomarkers, 47 biomarkers and 2240 patients from 30 studies were included.

Research results
These exosomal biomarkers had excellent diagnostic ability in various types of cancer, with good sensitivity and specificity. A total of 50 biomarkers and 4797 patients from 42 studies were included for the prognostic markers. We observed that exosomal biomarkers had prognostic values in overall survival, disease-free survival and recurrence-free survival.

Research conclusions
Exosomes could be potential biomarkers in cancer diagnosis and prognosis.

Research perspectives
Further large prospective studies are needed to clarify the performance of exosomal biomarkers in cancer diagnosis and prognosis, through exosomes can be potential biomarkers in cancer diagnosis and prognosis.

ACKNOWLEDGEMENTS

The work described in this paper was supported by grants from the General Research Fund, Research Grants Council of Hong Kong (CUHK462713, 14102714, 14136416 and 14171217), National Natural Science Foundation of China (8142730 and 81672323) and Direct Grant from CUHK to YC.

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P-Reviewer: Balaban YH, Teeraprasertsuk S

S-Editor: Cui LJ L-Editor: Filipodia E-Editor: Wu YYJ
