Editorial

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Impact of LC-MS/MS in Cancer Biomarkers Analysis

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ABSTRACT

Abbreviations: LC-MS/MS: Liquid Chromatography Mass Spectrometry; LC/GC-MS: Liquid Gas Chromatography-Mass Spectrometry; FD-LC-MS/MS: Fluorogenic Derivatization Liquid Chromatography Tandem Mass Spectrometry; Ran-GAP: Ran Specific GTPase Activating Protein; EF-Tu: Elongation Factor Tu; UPLC/TOF–MS: Ultra High-Performance Liquid Chromatography Time of Flight Mass Spectrometry; PLS-DA: Partial Least Squares Discriminant Analysis; PAA: Protein Antibody Array; AST: Aspartate transaminase; MALDI-MS: Matrix Assisted Laser Desorption Ionization Mass Spectrometry; RP-HPLC: Reversed Phase Liquid Chromatography; RCC: Renal Cell Carcinoma; HILIC-MS: Hydrophilic Interaction Liquid Chromatography Mass Spectrometry; LDA: Linear Discriminant Analysis; VCA: Variance Component Analysis

Editorial

Cancer is one of the leading causes of death in the modern age worldwide. Many cancers are associated with progression and abnormalities, but chemical biomarkers play a significant role in the diagnosis of cancer. Therefore, detection and identification of these biomarkers in various biological fluid samples play a significant approach in the detection and pathophysiology of cancer diseases. Various analytical techniques are reported and available in the literature for the detection and identification of various cancer biomarkers. Liquid Chromatography coupled with Mass Spectrometry (LC-MS/MS) is one of the advanced analytical techniques with high sensitivity and selectivity that have been utilized in the past few years for the detection, identification, and quantification of cancer biomarkers. In the present compilation, reports highlighted the significant impact of LC-MS/MS analytical techniques for the detection and identification of various cancer biomarkers in biological samples. Lung cancer is the leading cause of cancer-related deaths worldwide with a poor survival rate due to being diagnosed at a late stage. In the early-stage detection of lung cancer concerning clinical cost and disease prognosis at a defined location, biomarkers play a significant therapeutic benefit for early-stage cancer detection and identification [1]. Apart from early detection, body fluids analysis, such as blood, plasma, and serum also play a significant role in lung cancer diagnosis.

LC-MS/MS plays a major role in the analysis, identification, and well as thousands of complex compounds quantification in a biological matrix and proved to be a significant standard for this purpose [2]. Zeng et al. carried out the identification of lung cancer serum biomarkers through Liquid Chromatography coupled with Tandem Mass Spectrometry in Non-small Lung Cancer Cell patients with (n = 6) adenocarcinoma and (n = 23) squamous cell carcinoma. Apart from this, clinical control samples (n = 54) with nodules found on Computer Tomography were taken (Non-malignant lung cancer by biopsy confirmed) as well as from control patients (n = 106). On the other hand, serum samples were taken based on sex, smoking, and lung cancer tumor stage which pooled into sufficient pools, with (n = 9) cases of adenocarcinoma, (n = 6) cases of squamous cell cancer, (n = 8) cases of clinical control as well as (n = 8) cases of healthy control. The results indicate that 49 differentially abundant serum biomarkers such as gasoline, haptoglobin, alpha-1-acid glycoprotein 1, and N-acetylmuramyl-L-alanine amidase, were present in abundance in

pooled lung cancer cells and compiled by negative model of binomial regression with value ($p < 0.01$). The analysis of the functional method was carried out by Ingenuity analysis pathway tools which imply an abundance of inflammatory proteins that play a pivotal role in cell-cell signaling molecules, network interaction, and different physiological responses between two subtypes of non-small lung cancer cell patients.

This method proposed and confirmed that when it is fully validated it shows very significant results in the lung cancer diagnostic process [3]. Prostate cancer is the fourth most common cancer in Western Countries and the prevalence of this cancer is increasing day by day worldwide. The severity of prostate cancer is predominantly in males as well as the sixth major cause of death among males [4]. The chances of death survival are greatly increased by early diagnosis or by the biomarker identification involved in prostate cancer. One such biomarker is sarcosine which is a non-protein amino acid precursor of natural origin considered as an effective biomarker against prostate cancer. The increased level of sarcosine is of noticeable interest, especially in localized and metastatic tumor tissues. Sreekumar A. et al. carried out metabolomic profiles of sarcosine in the progression of prostate cancer by utilizing a combination of Liquid Gas Chromatography hyphenated with mass spectrometry (LC/GC-MS). The LC/GC-MS was successfully utilized and identified greater than 1,126 metabolites in 262 prostate cancer patients' specimens mainly tissue samples (n = 42) and urine and plasma match specimens' samples (n = 110) were assayed. The specimens' samples for analysis were biopsy-positive cancer patients (n = 59) and biopsy-negative control patients (n = 51) were analyzed, and the result obtained from studies may provide a determination of sarcosine compounds as well as other five metabolites named uracil, proline, leucine, glycerol-3-phosphate and kynurenine in biological samples.

Additionally, this study also reveals the prostate cancer progression concerning metabolite concentration and is helpful in benign prostate cancer differentiation, prostate cancer localization, and metastatic disease concerning metabolomic profiles [5]. Breast cancer is one of the leading causes of death among women, mostly in old age is breast cancer. However, many considerable studies are carried out, especially in mRNA profiling, proteomics studies, and breast cancer biomarkers but only a few molecular biomarkers are used for diagnosis and therapy due to their limited versatility [6,7]. Imai K et al. carried out their studies with Fluorogenic Derivatization Liquid Chromatography coupled Tandem Mass Spectrometry (FD-LC-MS/MS) with differential proteome analysis techniques among cancer cells patients and normal cancer cells patients. The studies revealed any changes in the protein chromatogram of breast cancer patients (n = 7) and normal cancer patients (n = 1) due to the presence of Ran Specific GTPase Activating Protein (Ran-GAP) in both cancer patient's cells. The characterization of cancer cells is due to the presence of Raf-1 kinase inhibitor whose abundance is higher as well as factors like Elongation Factor Tu (EF-Tu), Annexin-2, and Galectin-1 present in lower concentrations which implies that it could be helpful in the treatment of metastatic breast cancer. This method was advantageous for the diagnosis of metastatic breast cancer but further mechanistic investigation and studies at a larger scale are required [8].

Colorectal cancer is one of the leading causes of death worldwide and it is the second most common cancer in the Europe and USA in terms of mortality [9]. In China, the cases of colorectal cancer are increasing day by day and it takes place in fifth position in terms of death from colorectal cancer [10]. With the help of LC-MS and UP-LC-MS, detection and metabolite profiling are possible but UPLC-MS possesses better characteristics in terms of peak capacity, resolution, selectivity, specificity, and sensitivity as compared to LC-MS. Ma YL et al. carried out the urine metabolomic analysis of colorectal cancer patients through Ultra High-Performance Liquid Chromatography (UPLC) coupled with Time of Flight Mass Spectrometry (UPLC/TOF–MS) to investigate the LMCs in urine samples of colorectal cancer patients (n = 24) which was taken before and after surgery as well as healthy controls of the same age (n = 80). Several thousand peaks related to metabolites are detected by UPLC/TOF–MS and profiling of urinary metabolite through data interpretation was carried out by Partial Least Squares Discriminant Analysis (PLS-DA). The PLS-DA data shows result differences among the three examined groups (n = 3) and compounds MW 283 and MW 294 whose levels are noteworthy higher in before-surgery patients and after-surgery patients the levels of two compounds are significantly decreased due to their involvement in biochemical processes which is of particular interest. These results also state the potential biomarkers are helpful in the diagnosis of colorectal cancer but the sample size for analysis is relatively small [11].

The most prevalent cancer among all cancers is gastric cancer which has many deaths worldwide [12]. The gastric cancer treatment like chemotherapy and curative radiotherapy are typically ineffective but the majority of countries still have inexplicably high stomach cancer death rates, despite decades of progressively reducing incidence [13]. With the help of LC-MS/MS techniques and Protein Antibody Array (PAA) based proteomics along with genomics approaches Guo et al. investigated two gastric cancer cell lines named transcriptome and phosphoroscope in gastric cancer patients. Due to the presence of these gastric cancer cell lines, 17 gastric cancer cell lines of endoscopic biopsies were taken into consideration including five cancer cell lines named SNU1, SNU5, AGS, YCC1, and Kato III for phosphoroscope analysis. The main purpose of this study is to carry out the studies of phosphoproteins proteins which act as a major pervasive molecule of signaling and play a crucial role in the carcinogenesis pathway. The combined spectral data and integrative analysis data of transcriptome and phosphoroscope from all the cancer cell lines give a clear representation of molecular signaling pathways that are involved in gastric cancer [14]. Liver cancer is one of the third largest causes of cancer related death as well as the fifth most common cancer around the globe with a survival rate of less than 7% within five years [15].

The mortality rate of liver cancer predominantly in countries like Southeast Asia, Africa, Western Europe, and North America despite significant advancements in diagnosis and treatment early diagnosis is still challenging [16]. LC-MS possesses significant advantages like biofluids analysis, complex molecules characterization as well as reliable quantitative analysis of molecules. Chen F et al. by the application of LC-MS, serum metabolites analysis was carried out in liver cancer patients (n = 41; mean age = 55) and control subjects (n = 38; mean age = 35). The levels of Aspartate transaminase (AST) & ALT were analyzed between liver cancer patients and healthy control patients, instead, both were higher in the liver cancer group which suggests factors like drug abuse, hepatitis virus infection, and toxin ingestion were responsible. Apart from that, Principal Component Analysis (PCA) suggests 1-methyladenosine as a potent compound for liver cancer disease and this compound was also characterized as a most significant biomarker in liver cancer disease [17]. Oral cancer is one of the six major common cancers worldwide instead of not being diagnosed at an earlier stage the overall survival rate is <50% within 5 years and among Americans, it possesses a very high impact oral cavity disease affecting 38,000 Americans and 350,000 annually cases worldwide [18].

The main purpose of this study is to carry out the profile of oral fluid (whole saliva) samples of humans for proteomic analysis with the help of Matrix-Assisted Laser Desorption Ionization Mass Spectrometry (MALDI-MS) technique between cancer of oral patients as well as control patients and the level of 46 proteins or peptides were found notably different between these two groups. By the application of liquid chromatography (LC) followed by the C4 column, oral fluid samples were separated and monitored by MALDI-MS. The fraction samples were digested with the help of the LC-MS/MS technique to quantify the protein biomarkers from the oral cancer patient's clinical samples. This study also reveals that the oral fluids of saliva contain proteomic signatures that serve as a biomarker of oral cancer and once validated at a large clinical stage, it may be used in the future for diagnosis of human diseases such as oral cancer. This method was advantageous for non-invasive clinical diagnosis of oral cancer and informed further mechanistic investigation in oral cancer [19]. Bladder cancer (BC) is the seventh most common cancer in the United Kingdom, and it mainly occurs in the urinary system [20]. Instead of its continuous rise, the death rate of bladder cancer has not significantly changed in the past few decades, but the survival changes are highly increased by early diagnosis but only diagnostic tools like cystoscopy and urinary cytology are available currently [21]. Therefore, a non-invasive, accurate, and cheap method was adopted to identify a specific and potential biomarker for bladder cancer by metabonomic profiles.

The Liquid Chromatography Mass Spectrometry (LC-MS/MS) technique, was utilized successfully with a combination of Reversed-Phase Liquid Chromatography (RP-HPLC) and Hydrophilic Interaction (HILIC) chromatography separations techniques, followed by multivariate analysis data to profile samples of urine between bladder cancer volunteers (n = 27) and healthy volunteers (n = 32), from which the two metabolites of bladder cancer named as component I and carnitine C9:1 were identified. The study suggests that the component I level was higher as compared to carnitine C9:1 level in bladder cancer patients which serves as a potential biomarker for bladder cancer. The results obtained from multivariate data analysis of both group patients were up to 96.9 % specificity and 92.6 % sensitivity but the increased level of component I reason, and function are still unclear. This method is advantageous and far better in combined biomarker identification as compared to single biomarker identification but further confirmation against bladder cancer is still highly needed [22]. Kidney cancer or renal cell carcinoma (RCC) is one of the greatest interests among scientists in terms of its rarely discovered and it is the leading death cause in the USA [23]. The signs and symptoms of kidney cancer are equivocal which leads to late diagnosis but other procedures like nephrological screening act as diagnostic tools in kidney cancer, but non-invasive and newer techniques are highly needed in early-stage detection of kidney cancer in terms of diagnostic process [24].

By the application of Hydrophilic Interaction Liquid Chromatography coupled with Mass Spectrometry (HILIC-MS), urine metabolic profiling was carried out in urine samples of kidney cancer patients to quantify potential biomarkers of kidney cancer. The main purpose of this study is to carry out the urine sample analysis between renal cell carcinoma (n = 50) patients and healthy control patients (n = 13) for urine metabolomics analysis as well as Principal Component Analysis (PCA), Linear Discriminant Analysis (LDA) and Variance Component Analysis (VCA) were utilized for group data analysis. The utilization of this technique depends upon urine site collection and residual variation source of urine metabolomics analysis suggests a promising diagnostic approach towards renal cell carcinoma and acts as sufficient viable biomarkers. It also summarizes that the method can identify potent biomarkers, but the source variability needs to be eliminated for specific substances in urine samples of kidney cancer patients [25]. The above insight-evidenced reports suggest the impact and application of LC-MS/MS in the identification, determination, and characterization of cancer biomarkers as well as useful to the analyst, and clinical technicians for the utility of LC-MS/MS technique.

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Conflicts of Interest

The author declares no conflicts of interest, financial or otherwise.

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