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A REVIEW ON PROGNOSTIC BIOMARKERS – THROUGH THE LENS OF INDRIYA STHANA OF CHARAKA SAMHITA

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ABSTRACT

A biomarker, which is defined as a change in the components of tissues or bodily fluids, offers a potent way, to comprehend the range of chronic diseases and may be used in at least five different fields, including screening, diagnosis, prognostics, recurrence prediction, and therapy monitoring. Prognostic biomarkers are biological or clinical traits that assist in forecasting a patient's health outcome without therapy. They are used to identify patients who are more likely to have a certain outcome, such as illness recurrence or progression, or death. Numerous biomarkers have been created since Acharya Charaka's time. The use of biomarkers as a prognostic tool is demonstrated in the Indriya Sthana of Charaka Samhita. According to the well-known reference, "Charakasthu Chikisithe", Acharya Charaka has emphasized the use of a variety of biomarkers as a prognostic tool to prevent physicians from misjudging their patient's conditions. He explains dismal prognosis based on sputum, stool, and semen test in the Indriya Sthana. If a man's nisthyutam (sputum), purisham (stool), and retah (semen) sink into water, he has reached the end of his life. If the sputum has varied colors and sinks in water, the patient does not survive. This article examines the current information and research on sputum, stool, and semen as prognostic biomarkers.

Keywords: Biomarker, Sputum, Stool, Semen, Prognosis, Indriya Sthana, Arishta Lakshana

INTRODUCTION

Our classical texts tell us quite clearly that a Vaidya (physician) who treats an incurable illness loses his renown, fortune, and wisdom. Charaka Samhita, being the greatest treatise on Ayurvedic therapeutics, insists that a Vaidya must have a good understanding of the sadhya-asadhyatha (prognosis) of rogas (diseases) and start the treatment with the right knowledge to achieve success. Acharya Charaka has devoted an entire Sthana (section) in Charaka Samhita to make sure that a vaidya does not misjudge the condition of his patients and has placed Indriya Sthana before Chikitsa Sthana, presumably to guide the physician on when not to treat a patient. Understanding Indriya Sthana is essential for disease prognosis. Examining the chapters of Indriya Sthana reveals a variety of clinical conditions, and the signs and symptoms listed are significant predictors of the disease prognosis. A Vaidya (physician) who wants to know a patient's remaining lifespan should evaluate these signs and symptoms to ascertain the disease prognosis.

The Role of Biomarkers in Prognosis

Biomarkers play a crucial role in determining a patient's prognosis, by assisting physicians in the diagnosis, classification, and tracking of diseases. As an indicator of normal biological processes, pathogenic processes, or pharmacologic reactions to a therapeutic intervention or other health care intervention, a biomarker is described as "a characteristic that is objectively measured and evaluated." The body either produces the biomarker in reaction to disease or the afflicted organ (such as a tumor). Markers could be utilized for screening and risk assessment prior to diagnosis. A prognostic biomarker[1] is a biological or clinical trait that, independent of therapy, indicates the likelihood of a patient's health outcome (e.g., illness recurrence). It must be presumed that even during Acharya Charaka's period, the use of such biomarkers was widespread. Acharya Charaka has emphasized the use of a variety of biomarkers as a prognostic tool to prevent physicians from misjudging their patient's condition. Treatment should be planned after a complete examination of the disease and the patient, including the biomarkers. The patient should be evaluated using these biomarkers before communicating the remaining lifespan to the patient and their family. Various clinical conditions having a poor prognosis, which are fatal and are generally seen in patients at the end of their life, are explained in Indriya Sthana. He explains dismal prognosis based on nisthyutam (sputum), purisham (stool), and retah (semen) tests. If a man's sputum, faeces, and semen sink into water, he has reached the end of his life. If the sputum has varied colors and sinks in water, the patient does not survive.[2]

According to Acharya Sushrutha, a person who has only studied one science will not be able to make the right choice, hence it is essential to have multidisciplinary knowledge.[3] Based on Uhya Tantrayukti, a logical interpretation of the text for a better understanding of the science, an attempt has been made to understand the current relevance of using nisthyutam (sputum), purisham (human faeces or stool), and retah (semen) as prognostic biomarkers, as described in the Indriya Sthana of Charaka Samhita.

Sputum as a Prognostic Biomarker

Mucus that is coughed up from the trachea and bronchi is known as sputum. Sputum samples are typically used for cytological analysis of respiratory system, microbiological examinations of respiratory illnesses, and visual inspections.

Sputum – Visual Examination
Purulent sputum[4] is usually yellow or green, and it contains pus, which is made up of white blood cells, cellular debris, dead tissue, serous fluid, and viscous mucus. It is present in cases of pneumonia, bronchiectasis, lung abscess, or advanced-stage bronchitis. Patients can examine their sputum with the naked eye at home to observe the different colors.

Sputum - Microbiology
To check for infections including *Moraxella catarrhalis, Mycobacterium TB, Streptococcus pneumoniae,* and *Haemophilus influenza* and other pathogens, microbiological sputum samples are utilized.

Sputum - Cytology
Lung cancer, cystic fibrosis, and pulmonary exacerbations are among the illnesses for which sputum can be utilized as a prognostic biomarker. It has been demonstrated that sputum cytology[5] can identify premalignant alterations in high-risk individuals' years before lung cancer is clinically diagnosed. The idea that alterations in the cytology of bronchial epithelial cells represent the progression from inflammation to malignancy lends credence to this study. Since sputum contains airway epithelial cells and molecular changes found there are most likely to reflect tumor-associated changes or field cancerization brought on by lung smoking, sputum has been the focus of efforts to find non-invasive biomarkers for lung cancer. Morphology, allelic imbalance, promoter hypermethylation, gene mutations, and, more recently, differential miRNA expression are examples of molecular indicators derived from sputum that can be used to identify lung cancer.[6] People with cystic fibrosis can have their lung inflammation measured using biomarkers such as neutrophil elastase (NE), IL-8, TNF-α, and IL-1β.[2] It is possible to forecast upcoming pulmonary exacerbations using sputum biomarkers like sialic acid and hypoxanthine.[7]

Stool as a Prognostic Biomarker

Composition of Stool
Human faeces are the solid or semisolid remnants of food that the large intestine's microorganisms have further broken down, after it was unable to be absorbed or digested in the small intestine.[8] Additionally, it contains bacteria, dead epithelial cells from gut, and a negligible quantity of metabolic waste products including bacterially modified bilirubin. About 75% of fresh faeces is water, with 84–93% organic particles making up the remaining solid fraction. These organic solids include digestive secretions, mucus, small amounts of dry epithelial cells, insoluble calcium and iron phosphate salts, 2–25% protein or nitrogenous matter, 25% carbohydrate or undigested plant materials, and 25–54% bacterial biomass.[9]

Stool tests are a simple and non-invasive way to help diagnose a variety of gastrointestinal conditions, including inflammatory bowel disease (IBD), malabsorption syndromes, and gastrointestinal infections. Stool analysis can be performed using macroscopic, microscopic, chemical, immunological, and microbiological methods.

Macroscopic examination assesses the stool's color, consistency, quantity, shape, odor, and the presence of mucus or visible blood. Microscopic analysis identifies leukocytes, parasites, ova, and fat globules. Chemical tests detect occult blood, reducing substances, stool pH, and fecal fat, which aid in diagnosing bleeding disorders, carbohydrate malabsorption, and fat malabsorption. Immunological tests measure biomarkers such as calprotectin, alpha-1 antitrypsin, and pancreatic enzymes to evaluate intestinal inflammation, protein loss, and pancreatic function. Microbiological examination identifies infectious agents, including bacteria, viruses, and parasites, enabling accurate diagnosis and appropriate treatment of gastrointestinal infections.

Protein-based Stool Markers
Protein-based stool indicators seek to identify proteins released from bleeding or inflammatory tissue, or proteins specific to malignancy. M2 pyruvate kinase and fecal calprotectin are two of the most researched fecal protein indicators for colorectal cancer (CRC) screening.

A cytosolic protein called calprotectin[10] possesses antibacterial, antiproliferative, and immunomodulatory properties. It is present in stool, bodily fluids, and tissue samples. Infections, inflammation, and cancers all cause calprotectin levels to rise. As a result, it is a useful indicator of neutrophil efficiency. In inflammatory bowel disorders (IBD), fecal calprotectin levels rise. There is a correlation between the amount of fecal calprotectin and polymorphonuclear leukocyte infiltration of the intestinal mucosa. The M2-PK (M2 pyruvate kinase) test[11] is a stool test used to screen for colorectal cancer (CRC) by measuring the amount of M2-PK, an enzyme present in tumors.

DNA and RNA Based Stool Tests
The goal of the simple, non-invasive DNA- and RNA-based stool test is to find indicators of abnormal DNA or RNA from cancerous cells. This test's fundamental assumption is that neoplastic surface cells are expelled in faeces by colorectal cancer. The DNA or RNA of these cells is examined to identify various mutations that may have emerged during carcinogenesis.[12]

Guaiac Based Faecal Occult Blood Test
The Guaiac-based faecal occult blood test (gFOBT), which uses a peroxidase reaction to detect haemoglobin in faeces indirectly, was initially acknowledged as a reliable screening technique for the identification of colorectal cancer in 1996.[13] Several studies have shown that annual gFOBT screening reduces colorectal cancer-related morbidity and mortality by approximately 33% over a 13-year follow-up period, indicating its effectiveness in the early detection of colorectal cancer.[14]

Faecal Immunochemical Test (FIT)
FIT[15] uses antibodies specific to globin to detect human haemoglobin. One advantage of FIT over gFOBT is that it just requires one stool sample rather than three, and it does not require any dietary restrictions. A higher adherence rate and improved detection of advanced adenomas are demonstrated using FIT.[16]

Semen as a Prognostic Biomarker

Composition of Semen
Male gonads and male accessory glands secrete spermatozoa, which are found in semen, also referred to as seminal fluid. Seminal plasma is a fluid secreted by glands in the male urogenital tract in order to create semen. It includes small-molecule metabolites, lipids, glycans, inorganic ions, and biopolymers such as oligosaccharides, proteins, peptides, RNA, microRNAs, and cell-free DNA. The building blocks of antioxidant enzymes, necessary for healthy spermatogenesis include zinc[17] and selenium. The seminal vesicles are the source of the majority of the compounds in seminal plasma. In order to regulate sperm maturation, semen liquefaction, and motility, the prostate also secretes a fluid that contains lipids, citrate, and proteolytic enzymes. The bulbourethral glands[18] release mucin, sialic acid, and galactose to lubricate the semen and enhance sperm transmission efficiency. The polyamines putrescine, spermine, and spermidine maintain the alkaline pH of semen.[19]

Seminal Metabolomics

The developing field of seminal metabolomics focuses on the thorough examination of metabolites found in seminal fluid. Through groundbreaking metabolomics and its association with metabolic processes and biochemical pathways, metabolomics profiling provides insights into male infertility.

For males, prostate cancer is a serious health issue, and successful treatment and better results depend on early identification. Males with infertility seem to be at least twice as likely as the general population to acquire high-grade prostate and testicular cancer.[20] Research indicates that the identification of prostate cancer may benefit from the examination of semen biomarkers. To learn more about male infertility and its connection to cancer, semen and urological biomarker analysis is essential.

Sperm Chromatin Structure Assay (SCSA)

DNA damage and oxidative stress have also been identified as important contributors to male infertility and the development of cancer. Sperm chromatin deficiencies were evaluated using the Sperm Chromatin Structure Assay (SCSA) in the andrology lab of a tertiary care hospital in 12 healthy men and 37 cancer patients, including those with testicular cancer, Hodgkin's disease, non-Hodgkin's disease, and other neoplasms. The findings showed that cancer cases had far higher levels of DNA damage, underscoring the importance of assessing the integrity of sperm DNA prior to therapy.[21]

In one study, sperm DNA fragmentation and semen quality were examined between cancer patients receiving sperm banking and controls receiving Assisted Reproductive Technology (ART). The results showed that cancer patients had higher DNA fragmentation and lower sperm quality. According to this research, sperm DNA damage was more serious in cancer patients, regardless of the type of cancer, than in healthy, fertile men. This emphasises how crucial SCSA is for determining the quality of sperm in cancer patients.[22]

DISCUSSION

A biomarker is an evaluable and quantifiable biological measure that serves as an indicator of a certain pathophysiological condition. The diagnosis of conditions, tracking pathophysiological processes, stages of disease development or progression, evaluation of the disease prognosis, direction and monitoring of the therapeutic regimen, and detection of disease recurrence are all greatly aided by biomarkers and their quantification testing.

Clinical trials for biomarker-based medicines have advanced significantly. Novel biomarkers of various kinds can now be obtained through the use of genomic methods, epigenetics, metabolomics, transcriptomics, lipid-based analysis, protein research, etc. Many clinical trials are now being conducted to examine the effectiveness of biomarkers in different types of cancer. Cancer research is undergoing a revolution owing to the development of non-invasive biomarkers. The use of non-invasive biomarkers such as sputum, stool, and semen in small cell lung cancer, colorectal cancer, and prostate cancer is currently on the rise. Finding and confirming these biomarkers promises early identification, real-time monitoring, and individualized treatment plans in the age of precision medicine.

Acharya Charaka has dedicated the Indriya sthana in Charaka Samhita for understanding the prognosis of diseases, and he believes that a Vaidya(physician) must be well-informed about the sadhya-asadhyatha (prognosis) of rogas (diseases) and should start treatment with proper information in order to achieve success. He recommends the evaluation of biomarkers such as nisthyutam (sputum), purisham (stool), and retah (semen) in order to determine the prognosis and states that a man has reached the end of his life if his retah (semen), purisham (stool), and nisthyutam (sputum) sink into water. The patient does not survive if the sputum has different colors and sinks in water. Although sputum, stool, and semen are very different biological specimens, they all offer important clinical information. Sputum analysis is critical in detecting respiratory infections, lung malignancies, and other non-cancerous lung diseases; stool is essential for gastrointestinal and systemic infections; and semen is mainly used to assess male infertility and reproductive tract health. Changes in the density (thickness, consistency, or volume) of semen, faeces, and sputum provides vital clinical insights. Semen density changes typically show up as either too thick or too watery. Variations may be normal, but abrupt or ongoing changes in density frequently indicate underlying illnesses, inflammation, hydration problems, or even changes in fertility. Sputum's consistency and color alter in response to any respiratory tract irritation, infection, or inflammation. The main factors influencing stool density and consistency range from watery to hard/dense or jelly-like, depending on nutrition, transit time through the gut, hydration, and any current pathology. From ancient times to the present, the analysis of the body's secretory and excretory products has been crucial for the diagnosis and prognosis of illness. Our Acharyas used extensive non-invasive observational and qualitative procedures to assess bodily fluids. Instead of using quantitative laboratory testing, these methods mostly depended on the senses to identify imbalances in the three Doshas (humor). The foresight of Acharya Charaka should be appreciated in forecasting nisthyutam (sputum), purisham (stool), and retah (semen) as prognostic biomarkers for the gross pathologies mentioned in Indriya Sthana.

CONCLUSION

The Charaka Samhita is regarded as the foremost scripture on Kayachikitsa (clinical medicine). According to Acharya Charaka, a person who is vicharajna (thinker) and arthajna (knower of meanings) will become a chikitsakushala (efficient in treatment). He emphasized that a Vaidya (physician) who studies medical texts critically and applies their principles judiciously can promote both the longevity and well-being of patients. Thousands of years ago, with limited technical capabilities, Acharya Charaka, through his par excellence observation, had put forth the usage of nisthyutam (sputum), purisham (stool) and retah (semen) for the prognosis of various disorders, which seems to be valid even now. Acharya Charaka's patient-friendly techniques are demonstrated by the current trend of using non-invasive biomarkers such as sputum, stool, and semen to aid in early cancer identification, precise subtyping, and individualized treatment plans to enhance patient outcomes.

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