

Serum Tumor Markers: A Study on Their Rational Use in Various Cancers

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ABSTRACT

Background: Cancer is among the leading noncommunicable diseases and its screening, diagnosis, management, monitoring, and relapse involve the use of tumor markers. Tumor marker requisition adds to a major financial burden if not used rationally. **Aim and Objectives:** The aim was to study the rational use of tumor markers in various cancers with objectives to do requisition analysis of tumor markers with the existing national guidelines by the Indian Council of Medical Research (ICMR) and to assess its financial impact. **Materials and Methods:** A total of 355 cases were screened and 221 were included in the study. The patient's laboratory requisition form raised by the ordering physician as a part of the screening, diagnosis, management, monitoring, and relapse for different conditions including cancers were studied retrospectively over a period of 5 months, and data were analyzed. **Results:** Two hundred and twenty-one requisitions for various tumor markers were ordered for screening, diagnosis, management, monitoring, and relapse of various cancers and other conditions. Only 10%–30% of requisitions were found as per the laid down guidelines of the ICMR for different cancers. Carcinoembryonic antigen was ordered in only 20% requisitions as per the ICMR guidelines but has affected maximally in terms of test cost by adding up 88% to the budget of the test. **Conclusion:** Rational use of tumor markers in different cancers can cut down the cost factor directly. It prevents the physician in overdiagnosing due to multiple requisitions in diagnosed cancers and hence avoiding undue medical procedures thus further reducing the financial burden on the patients and their family.

KEYWORDS: *Diagnosis, financial burden, requisitions, tumor markers*

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INTRODUCTION

Cancer is emerging as one of the leading noncommunicable diseases worldwide with an estimated incidence of 18.1 million new cases in 2018 as per the International Agency for Research on Cancer.^[1] The National Institute of Cancer Prevention and Research report 2018 states that in India, every year, 1,157,294 new cancer patients are registered.^[2] Among all cancers, the most common cancers in which tumor markers are being ordered are hepatocellular cancer (HCC), germ cell cancers, breast cancer, colorectal cancer, prostate cancer, pancreatic cancer, etc.^[3] The various steps in the management of cancer right from screening to treatment and follow-up

involve battery of investigations; one being the use of the tumor markers.


Tumor markers are biochemical substances that may be present in abnormally high concentrations in body fluids or tissues from patients with cancer. They are surrogate indicators that can increase or decrease the clinical suspicion for a relevant clinical event and can aid in the management of cancer.^[4] They range from simple molecules like catecholamines to complex

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protein molecules like hormones, enzymes, and gene products.^[5] They can be measured quantitatively by chemical, immunological, genomic, or proteomic methods. Ideal tumor marker has not been identified yet in clinical utility, however few markers have been recommended, for example, tissue-based estrogen and progesterone receptors for breast cancer by the American Society of Clinical Oncology.^[6]

Tumor markers have an additional role in the workup and its management, but it adds a significant financial burden if requisition and interpretation are not done in a correct way.^[7] The economic burden on the patient and family has a huge impact on their psychological states.

No previous studies have been done in the Indian scenario in this regard. This study was undertaken with the aim to study the rational use of tumor markers in various cancers in our tertiary care hospital as per national guidelines on screening, diagnosis, management, monitoring, and relapse of various cancers issued by the Indian Council of Medical Research (ICMR) mentioned in Table 1, with an objective to assess its financial impact.

MATERIALS AND METHODS

Study design

This was a retrospective observational study.

Study population

The study population included the patients who were advised to undergo various tumor markers' testing in our laboratory for different medical conditions based on the clinical notes by the ordering physician.

Study period

The data were collected over a 5-month period from February 2019 to June 2019 in our tertiary care institute.

Inclusion criteria

A total of 355 cases were screened and 221 were included in the study. The cases which had been ordered investigations of tumor markers as listed in Table 2 were included in the study.

Exclusion criteria

The cases lacking the information of provisional diagnosis and valid signature of the physician with stamp were excluded from the study. The samples which were visibly hemolyzed, icteric, and lipemic were also not included in the study.

Ethical issues

All efforts were made to ensure the confidentiality of the records. Samples sent to the laboratory were rendered unlinked anonymous. Approval for publication of the findings was obtained from the Institutional Ethical Committee (AFMC letter number IEC/2020/287/dated August 6, 2020).

Methodology

Blood samples received in the laboratory were processed in the centrifuge to obtain serum. The samples were then quantified using automated mini VIDAS multiparametric immunoassay system based on enzyme-linked fluorescent assay^[8] after due calibration along with control samples. The results were analyzed using Statistical Package for the Social Sciences 20.2. The cost of each test is shown in Table 2.

Table 1: List of various tumor markers and their recommended utility as per the Indian Council of Medical Research guidelines

Tumor markers	Recommendations as per the ICMR guidelines
CEA	Follow-up and recurrence of colorectal carcinoma Diagnosis and monitoring of pancreatic cancer Not recommended in gastric cancer Optional marker in cholangiocarcinoma
CA125	Screening of ovarian cancer Monitor ovarian, endometrial, peritoneal, or fallopian tube cancer Check for recurrence of cancer
CA15.3	Clinical utility and monitoring not yet established in breast cancer
CA19.9	Diagnosis and monitoring pancreatic cancer Follow-up and recurrence of colorectal cancer Not recommended in gastric cancer After biliary decompression in jaundice patient in cholangiocarcinoma
hCG	Diagnosis of choriocarcinoma
AFP	Initial workup of hepatocellular carcinoma but not a part of diagnostic algorithm Elevated in cholangiocarcinoma, other colon cancers, and yolk sac tumors

ICMR, CEA: Carcinoembryonic antigen, CA: Cancer antigen, hCG: Human chorionic gonadotropin hormone, AFP: Alpha-fetoproteins

Table 2: Tumor markers: Estimated cost per test

Tumor markers	Estimated cost per test (rupees)
CEA	450
CA125	500
CA15.3	500
CA19.9	500
hCG	275
AFP	275

CEA: Carcinoembryonic antigen, CA: Cancer antigen, hCG: Human chorionic gonadotropin hormone, AFP: Alpha-fetoproteins

RESULTS

In our study, 221 tests of different tumor markers were ordered for screening, diagnosis, management, monitoring, and relapse of various cancers and other conditions as per the percentage distribution shown in Figure 1. Only 10%–30% of requisitions were found as per the laid down guidelines of ICMR for different cancers as shown in Figure 2, which has increased the expenses by 75% in total. The cost-wise breakdown of various tumor markers has been shown in Figure 3. Carcinoembryonic antigen CEA was requested only in 20% cases as per the ICMR guidelines, while it has a financial impact of 88% of the total cost of CEA. Alpha fetoprotein (AFP) was most commonly ordered for screening and diagnosis of hepatocellular carcinoma HCC, however 33% of the requisitions were not as per the ICMR guidelines and adding around 80% cost to the whole expenditure of the test.

In our study, we observed that out of 45 tests for cancer antigen 19.9 for different conditions, only 24.44% tests were included as recommended panel by the ICMR for pancreatic cancer, cholangiocarcinoma, and colorectal cancer contributing to 75.66% of the added cost to the test budget. Hundred percent of the CA 15-3 tests ordered for carcinoma breast which were not as per the ICMR guidelines. About 27.7% of human chorionic gonadotropin tests were requested for choriocarcinoma and germ cell tumors as per the guidelines while the requisitions ordered for conditions such as adnexal cysts, motor neuron disease, and dysphagia which were not as per the ICMR guidelines have inflated the budget of the test by 72.22%. Forty-nine percent of total requisitions of CA 125 were not found as per guidelines issued by the ICMR and adding up 46.88% to the cost.

We observed that CEA has added maximally to the cost, while the requisition in 88% cases were not as per ICMR guidelines.

DISCUSSION

Screening, diagnosis, management, monitoring, and relapse of various cancers may require the aid of

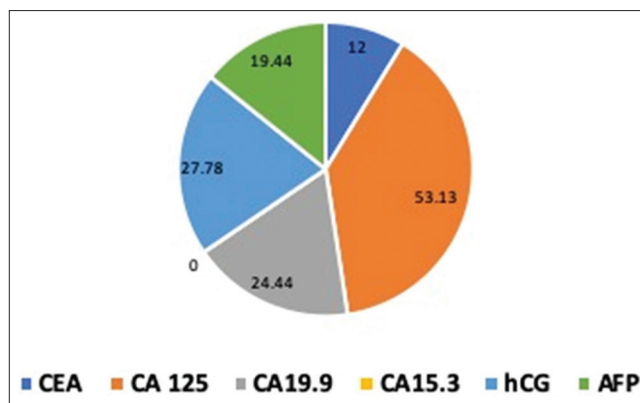


Figure 1: Percentage of various tumor marker requisitions as per the Indian Council of Medical Research guidelines

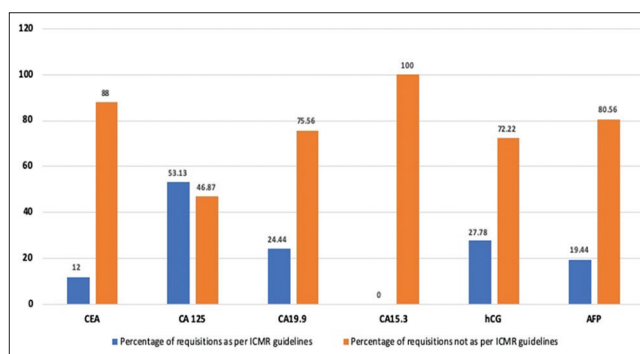


Figure 2: Percentage requisitions

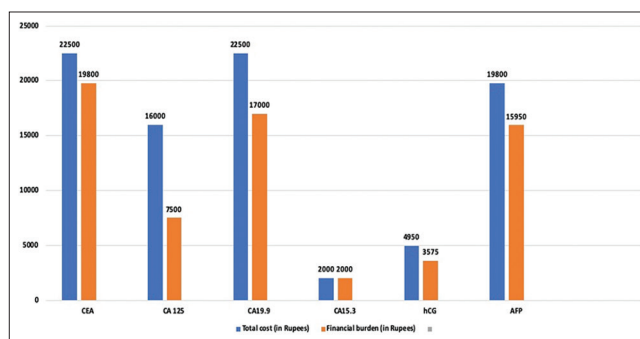


Figure 3: Financial impact

tumor markers. In our study, we have included tumor markers as recommended by the ICMR. As the tumor markers have an additional role, rational use of tumor markers is the key for preventing the financial burdens on the patients and their families. In this study, we also observed that AFP was the most common requisition among all, followed by CEA and others.

Carcinoembryonic antigen

CEA is an oncofetal antigen widely utilized for follow-up and assessing the prognosis in colorectal cancer as per the ICMR^[9] along with CA 19-9; very limited role has been found in the screening and diagnosis. The utility of CEA lies in monitoring pre- and

postoperative levels in colorectal carcinoma and cholangiocarcinoma,^[10] while we observed that CEA was requested for 70% cases of hepatic and gastric cancers contrary to its recommendations by the ICMR causing additional burden of Rupees (Rs) 450/test/visit to the patient and making up an additional financial impact of around Rs 19,800.00 (44 out of 50 tests at Rs 450) to the laboratory budget.

Cancer antigen 125

It is a tumor-associated glycoprotein of about 200 kilo Dalton which has a sensitivity of about 80% in ovarian cancers. We also observed that CA 125 was requested in six males as a part of routine checkup and in cases of acute liver failure, chronic kidney disease, and colorectal cancer, which is a strongly discouraged requisition in men recommended by the National Academy of Clinical Biochemistry in a study by Sturgeon *et al.*^[11] The only role of pre- and postoperative CA 125 levels has been demonstrated in a study by Basu *et al.*^[12] in colorectal carcinoma in males, and we also found one similar requisition in our study. In addition, 20 tests of CA 125 were asked in hepatic and pancreatic cancers and other benign conditions with a very limited role in diagnosis and management causing an additional burden of about Rs 500/test to the patient ultimately adding Rs 7500.00 to the laboratory budget.

Alpha-fetoproteins and human chorionic gonadotropin hormone

AFP is synthesized from the liver of the fetus and hCG is synthesized by the placenta. The ICMR recommends both the markers for yolk sac tumors and choriocarcinoma while AFP only for testicular cancer and screening of HCC.^[13,14] Even though the AFP has a 41%–65% sensitivity and 80%–94% specificity in HCC, still it is being employed as a routine test adding to the total cost.^[15] We also saw an increased trend of AFP in other conditions such as esophagus, gastric cancer, and deep vein thrombosis which is around 36% of the total AFP requisitions causing an additional expenditure of around Rs. 275/test to the patient and burdening the laboratory with additional Rs. 19,800.00. Not only the financial burden but also the overuse of the test in a laboratory may deprive the needy patients from being getting benefit from the same.

Cancer antigen 19-9

CA 19-9 is a tumor-associated mucin glycoprotein antigen present in the pancreas, biliary ductular cells, gall bladder, colon, and other tissues, which is also related to Lewis blood group protein. It is mainly utilized for monitoring the treatment response in pancreatic cancer with a sensitivity of 70%–90% and specificity of 68%–91%. In our study, we found that CA 19-9 has

been advised in 25 % cases of pancreatic and colorectal cancers along with cholangiocarcinoma which follows ICMR recommendations.^[16,17] We also noted that 75% of the tests were requested for gastric and hepatic cancer, breast cancer, ovarian cysts, and diseases like motor neuron where no such recommendations^[18] are present causing undue expenditure amounting to Rs. 500/test adding Rs. 17,000/-to the total financial budget.

Cancer antigen 15-3

Cancer antigen 15-3 is found in particularly breast cancer cells and is made up of protein. As per the ICMR, the clinical utility in diagnosis has not been established,^[19] but its use in monitoring has been studied in a study by Fejzić *et al.*^[20] In our study, we found four requisitions for postoperative breast cancer, ovarian cancer, ascites, and amyloidosis adding to unnecessary further investigation and increasing the total budget to Rs. 2000/-with an additional cost of Rs. 500/test to the patient.

On analyzing all the tumor markers, we observed the total financial impact of about Rs. 87,750.00 over 5 months on the institution due to all the requisitions, however Rs. 65,825.00, which is around 75% of the total amount, have been spent on the tumor marker investigations not as per the ICMR guidelines. ICMR, however, also states that these guidelines have been framed as per the existing evidence and expert in the field and emphasize the use based on clinical scenarios. The use of the tumor markers may be scrutinized based on the existing guidelines which can cut the extra cost burden to the patient as well as to the institution.

CONCLUSION

Tumor markers aid in the screening, diagnosis, management, monitoring, and relapse of various cancers. These markers may be advised judiciously as per the recommended guidelines of the ICMR and clinical condition of the patient. If suggested judiciously, it prevents the physician in overdiagnosing due to multiple requisitions in diagnosed cancers and hence avoiding undue medical procedures, thus reducing the financial burden on the patients, their family, and the institution. It is also recommended that the ICMR should frame the guidelines for the other tumor markers also which are being used in the clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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