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Abstract: Background
Mucinous breast carcinoma is a tumour characterized by a large amount of extracellular mucin. There are two main subtypes: pure, which is more frequent, and mixed. It represents about 4% of all invasive breast cancers and is more common in perimenopausal and postmenopausal women. The objective of this study was to investigate the epidemiology and tumor characteristics in a tertiary single center, determine the long-term survival and identify aggressive clinical presentations such as larger tumor, more positive lymph nodes, and the characteristics of more advanced stage cases.
Materials and methods
We conducted a retrospective analysis in our database between 2008 and 2018. We calculated disease free survival and overall survival at 5 years of follow-up and compared the results with 5-years OS and DFS of invasive ductal carcinoma in the database during the same period
Results
We found 157 Cases of MC, including 81 cases of PMC and 76 Cases of MMC. Median follow-up was 35 months. We found little difference between the two groups in terms of triple-negative or Her2-enriched profiles, but the differences were statistically significant in terms of luminal-A tumours (more in PMC patients, 61.84%, versus 35.53% in MMC patients) and luminal-B tumours (more in MMC patients, 61.84%, versus 38.27% in PMC patients).

Cover Letter

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Dear Editor:

I am pleased to submit an original research article entitled “Mucinous Breast Cancer: A narrative Review of the Literature and a Retrospective Tertiary Single-Centre Analysis” for consideration for publication in your journal. We have treated some cases of this mucinous breast cancer, or MC, a rare form of neoplasm and we have questioned ourselves what could be the best clinical management, since there are no guidelines.

In this manuscript, we conducted a retrospective analysis in our database between 2008 and 2018 and made a narrative literature review in order to highlight the most common clinical presentation, disease-free survival and overall survival, current clinical management and treatment strategies.
Because of the rarity of this tumor, there are no guidelines available and very often treatment strategies are based on previous cases and narrative literature review.

We believe that this manuscript is appropriate for publication in “The Breast” because it explores various aspect of a rare mucinous tumors and your journal is a leading journal in the field of breast tumors management.

This manuscript has not been published and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose.

Thank you for your consideration!

Sincerely,

Dr. Federico Frusone
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TITLE PAGE

Title: Mucinous Breast Cancer: A narrative Review of the Literature and a Retrospective Tertiary Single-Centre Analysis.

Running Title: Mucinous Breast Cancer

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Abstract

Mucinous breast carcinoma (MC) is a rare neoplasm characterized by a large amount of extracellular mucin. There are two main subtypes: pure (PMC) and mixed (MMC).

We conducted a retrospective analysis in our database calculating disease-free survival (DFS) and 5-year overall survival (OS). We found a global 92.07% OS (higher in MMC group and statistically significative) and a DFS of 95.27% (higher in MMC group but not statistically significative).

Keywords

Mucinous Carcinoma Breast; Breast Cancer; Breast Surgery; Breast Conservative Surgery; Mastectomy; Invasive Breast cancer; Breast Neoplasms; Mastectomy; Adenocarcinoma, Mucinous

Introduction

Epidemiology

Mucinous breast cancer (MC) represents about 4% of all invasive breast cancers[7] and is more common in perimenopausal and postmenopausal women. It has a better prognosis compared to ductal and lobular breast cancer[6].

Pure mucinous breast cancer (PMC) represents about 2% of all malignant breast tumours. In a retrospective series of 11,400 PMC cases, the median age at diagnosis was 71 years versus 61 years observed in patients with infiltrative ductal carcinomas[15]. Metastatic disease rate ranges between 12% and 14% in the largest case series reported[15]; the prognosis is better than breast carcinoma of no special type[10]. The 10-year survival rate is about 90.4%[16]. From a histological point of view, it is important to differentiate PMC from mixed types of ductal carcinoma with mucinous component (mixed mucinous breast cancer - MMC), which occur in only 2% of cases. In fact, the latter have an identical prognosis compared to non-mucinous tumours[16;17]. Axillary lymph nodes are rarely involved; nevertheless, a nodal metastatic disease can definitely worsen the survival rates and it is considered as one of the most important prognostic factors[17].

Pathology of MC

Mucinous breast carcinoma is a tumour characterized by a large amount of extracellular mucin. There are two main subtypes of MC: pure (PMC), which is more frequent, and mixed (MMC)[1]. To be defined as PMC, a carcinoma must be made up of at least 90% of mucinous tissue. In most cases such a cancer is both ER- and PR-positive, but AR-negative[5]. PMC may be classified as hypocellular (PMC-A) and hypercellular (PMC-B). The hypocellular variant may have a different growth pattern (tubular, cribriform, cord-like, papillary or micropapillary). The hypercellular variant, however, shows only one growth pattern, it spreads outwards as solid nests[3]. The mean metastasis rate is about 15%[14] and the prognosis is better compared to breast cancer of no special type[15]. Generally, PMC growth velocity is slow, but it is often diagnosed when large diameters have been reached[18].

MMC contains less than 90% of mucinous components with the expression of other architectures such as lobular or ductal breast cancer-like (both in situ and invasive)[2]. Lei et al. proposed that MMC be subdivided into two groups based on the amount of mixed mucinous component[10]. According to these authors, it is possible to distinguish a partial mixed mucinous breast carcinoma or pMMC (containing < 50% of mucinous elements) and a main mixed mucinous breast carcinoma or mMMC (cointaining from 50% to 90% of mucinous elements) as explained in the Table below (table 1).

Diagnostic procedures

From a radiographic point of view, the appearance of MC could be similar to benign lesions (for instance, clear margins and isoechoic compared to the surrounding subcutaneous fat in ultrasonography and round shape in mammography). So, the differential diagnosis in these tumors is crucial.

MC in most cases appear at mammography as a low-density, round or oval shaped mass, with clear edges. Tumor borders could vary from microlobulated (high mucin content) to irregular or spiculated (low mucin content). Consequently, the mucin content is correlated with peripheral characteristics[11]. In some cases, MC could be mammographically occult or show non-mass mammographic findings, such as calcifications, occultation or focal asymmetries[12].

At ultrasound, MC appears as a round or oval mass, isoechoic or hypoechoic compared to the surrounding subcutaneous fat, often with posterior acoustic enhancement and internal echoes, with cystic or solid components[12]. Usually PMC shows heterogeneous internal echoes more frequently compared to MMC. In some cases, PMC could present sound attenuation.

The MRI appearance is usually a circumscribed mass with high signal intensity in T2-weighted sections, low intensity in DWI phases, gradual and persistent enhancement and benign-appearing kinetics. So, even in MRI it may be difficult to differentiate a MC from a benign lesion. However, some MRI characteristics, such as the presence of enhancing internal septations and higher apparent diffusion coefficient (ADC), could help to differentiate MC from benign lesions, such as fibroadenomas and low-grade phylloides tumors[13].

In the differential diagnosis between MC and benign breast tumors it is therefore important to correlate mammographic, ultrasound and MRI findings with clinical characteristics. It is also important to distinguish between PMC and MMC, since PMC usually shows a better prognosis and a lower lymph node metastasis rate.

Genetics

MC may not only be identified from the histologic pattern, but has also a molecular identity which differs from that of invasive ductal carcinoma[9]. Furthermore, MC seems to have a different molecular pathogenesis from that of ductal and lobular breast cancer and a lower genetic instability than these tumors[8].

In a recent study, the genomic profiles of 59 breast cancer samples of 10 histological special types were evaluated[23]. An interesting result was that some of the special types with the best prognosis (not only mucinous but also adenoid cystic and tubular carcinomas with neuroendocrine features) presented with the lowest levels of gene copy number changes. Moreover, these special types lacked 1q gains and 16q losses, which represent hallmark features of low-grade invasive ductal carcinomas, thus suggesting that the pathways driving the carcinogenesis of these rare entities may be unique. Supporting this hypothesis, mucinous carcinomas of the breast lack PIK3CA and AKT1 mutations, which is in contrast with the high frequency (up to 45%) at which PIK3CA mutations occur in luminal breast cancers[24].

Another difference between MC and common ductal carcinoma was found by Toikkanen et al[25]. They reported that nearly all MCs have a normal diploid stemline unlike that of common ductal carcinoma. Aneuploid tumors tend to be of higher grade and stage than diploid tumors. Following the pattern, Jambal et al. developed a human breast cancer cell line called BCK4, which they proposed as the unique model for a clearer study of the phenotypic plasticity, hormonal regulation, optimal therapeutic interventions and metastatic patterns of MC.

Treatment

Mucinous breast cancer, like other “special histology” breast cancers, often presents unique clinical behaviours.
Unfortunately, the rarity of these entities has impaired the possibility of an extensive clinical evaluation.

Most of the information on outcome and treatments comes from small series and case reports. Therefore, clear recommendations concerning clinical management are still lacking.
Assessing and planning the most appropriate procedure is nonetheless crucial.

The first guideline to describe a separate treatment for “special histologic types” came from the 2013 St. Gallen consensus conference, in which endocrine therapy was recommended for endocrine-responsive “special histological types” (i.e. mucinous) and cytotoxic therapy recommended for endocrine-nonresponsive special types.
The 2014 NCCN Guidelines include specific treatment recommendations for the favourable mucinous histotypes. If the tumour is hormone receptor-positive and in the absence of nodal involvement, adjuvant endocrine therapy can be avoided where tumor size is less than 1 cm. If T is between 1 and 3 cm, endocrine therapy should be considered, and it is recommended for T greater than 3 cm. In cases with nodal involvement however, endocrine therapy with or without chemotherapy is indicated.
In the current guidelines there are no significant changes from this point of view.

From our review of the published literature, it seems clear that PMC and MMC should be considered as separate entities from nodal involvement point of view. Despite the fact that PMC tends to remain localized, the mixed forms have a greater capacity to metastasize to lymph nodes (25% Vs 10%[17] with a mean of 12-14%[21,22]). For this reason, from a surgical point of view, the mixed forms often require an axillary dissection as well.

Nevertheless, we consider surgery to be the main treatment strategy supported by adjuvant chemotherapy and radiotherapy.
Even though it is somewhat unusual, some authors have suggested administering neoadjuvant chemotherapy (NAC) in the most difficult cases of invasive mucinous carcinoma[26]. This is due to the fact that MC tumours are more frequently estrogen receptor-positive. Therefore, NAC based on a taxane-containing regimen along with an anthracycline or carboplatin plus surgery after about four weeks could prove to be the best option guaranteeing a longer disease- free survival (DFS).

Clinical outcomes

Looking at clinical outcomes it appears clear that MC and invasive ductal carcinoma (IDC) could be considered as two separate entities and that axillary lymph node involvement has clearly been discovered to be the most important prognostic factor in both.

As shown by Bae et al., MC patients have better DFS than IDC patients even though the OS seems to be quite similar. Adjuvant therapy and nodal status represent the most significant predictors of prognosis, more so than histologic subtype[1].

MC patients, when compared to IDC patients, presented with a lower N stage, higher ER and PR expression and a more favourable histologic grade. Pure MC patients showed better DFS rates than those of IDC patients, but not significantly different from mixed-type MC.

PMC has a better OS compared to both IDC and mixed-type MC.

On the other hand, considering the mixed-type MC patients alone, the DFS compared to that of IDC patients was not significantly different. Finally, in a stage-matched analysis for DFS and OS, MC patients showed a better survival than did IDC patients[1].

Interestingly, Di Saverio et al. used tumor size as an independent prognostic indicator, but it was considered a less valuable indicator, when compared to nodal status and age in MC cases. In fact, according to the AJCC staging system, tumor size may not be a significant factor because of mucin, which comprises the majority of the tumor volume[20].

Looking at some specific collections, the sample presented by Di Saverio et al.[15] may be regarded as the largest. In 11400 PMC patients retrospectively reviewed, the 5-year overall survival was established to be 94%, higher than IDC (82%) and the difference resulted statistically significant. In this review, the most significant prognostic factor was nodal status, followed by age, tumor size, progesterone receptors and nuclear grade. For this reason, N stage should be always assessed in patients affected by MC, with the exception of patients with early breast cancer without expression of vascular or lymphatic invasion, in whom axillary surgical staging could be avoided[27].

In the Bae et al[1] review 268 patients with MC were collected and compared to 2455 patients with invasive ductal carcinoma. MC patients had a 5-year DFS rate of 95.2% (vs 92% of IDC), a 5-year OS of 98.9% (vs 94.9% of IDC) and overall, MC showed a better survival than IDC.

Cao et al, in 2012[19] analysed 309 patients with PMC and found a 5-year DFS of 89%, a 5-year OS of 95%, and a better OS and DFS rate compared to IDC.

Tseng et al, in 2013, examined data from 93 patients with MC compared with 2,674 IDC patients. The 10-year overall survival rate was 94.5% vs 86% for the MC and IDC patients, respectively (P = 0.042), indicating that MC had a better long-term outcome than IDC, with statistical significance.

From our literature review, OS and DFS vary according to different studies. However, when a comparison is drawn between studies, the mean OS is 92% and mean DFS is 89% (table 2).

Apart from that, it is important to differentiate PMC from mixed subtypes. In this case it is fundamental to consider the nodal involvement frequency of the mixed subtypes (25% vs 10% according to Skotnicki[17]). The same group calculated ten-year DFS rates of 85.7% for PMBC and 65.0% with MMBC; the difference is statistically significant (log-rank test, $p < 0.02$)

Materials and methods

We searched the Humanitas Research Hospital database for patients between 2008 and 2018 with the following diagnoses: pure breast cancer and mucinous breast cancer. The 5-year OS and DFS were then calculated by means of a log-rank test.

Data regarding patient and tumour characteristics, and pre-operative and post-operative data were analyzed with the SPSS software package. Continuous variables were presented as medians and ranges, dichotomic variables as percentages. Student's T-test was used for continuous variables, and the Chi-square test or Fisher's exact test for categorical variables. Survival was estimated in terms of disease-free survival (DFS) calculated in months from surgery to recurrence and in overall survival (OS) from surgery to death or last follow-up. The two-sided significance test was used for statistical comparisons, with a p-value of ≤0.05 being considered as statistically significant. The log rank test was used to compare the survival distributions of the two groups.

Results

Our data are summarized in Table 3.

From our total of 157 cases, we found 81 cases of PMC and 76 cases of MMC. The median follow-up was 35 months (range 1-353). The overall 5-year OS was 92.07% and higher in MMC group (96.84% versus 87.10% in PMC group, $p < 0.05$). The overall 5-year DFS was 95.27% and slightly higher in MMC group, but non-statistically significant (96.43% versus 94.05% in PMC group, $p = 0.182$) (fig. 1, 2).

The mean age at diagnosis was 64.4 years and above in the PMC group (69.1 versus 59.4 in the MMC group, $p < 0.001$).

Regarding surgical treatment, most patients underwent breast-conservative surgery (78.34%), but mastectomy was more utilized in MMC patients (32.89% versus 11.11% in the PMC group, $p < 0.001$). This was confirmed by the data on tumor diameter, which was slightly greater in the MMC group (22.46 mm versus 18.75 mm in PMC group), even though the difference was not statistically significant ($p = 0.691$). Regarding axillary surgery, 68.15% of all patients underwent SLNB, and the percentages were similar in the two groups (67.90% in PMC and 68.42% in MMC) and 28.55% of the patients underwent ALND (primary or secondary to SLNB). More MMC patients underwent ALND than did PMC patients (43.42% vs 41.81% in PMC group). This reflects on the percentage of axillary metastases, which was greater in MMC patients (31.58% vs 11.1% in the PMC group).

Regarding adjuvant treatments, more MMC patients had adjuvant chemotherapy administration than did PMC patients (31.58% vs 7.41%, $p < 0.001$). However, there was no difference between the two groups regarding adjuvant radiotherapy (83.95% in the PMC group and 84.21% in the MMC group).

Finally, regarding the biological profile, we found little difference between the two groups in terms of triple-negative or Her2-enriched profiles, but the differences were statistically significant in terms of luminal-A tumors (more in PMC patients, 61.84%, versus 35.53% in MMC patients) and luminal-B tumors (more in MMC patients, 61.84%, versus 38.27% in PMC patients).

Discussion

Our data regarding 5-year OS and DFS is a little lower than that in other clinical studies. We found a 92.07% 5-year survival rate in MC patients, this being influenced by the age of our patients. In fact, in our database the median age was 64.4 years, 18.47% of the patients were aged 80 or above (29 cases) and many of them died from other causes. In the subgroups, we found a better OS in MMC group compared to that in the PMC group, and the difference was statistically significant ($p < 0.05$), but also influenced by age at diagnosis (higher in PMC patients, 69.1 years versus 59.4 years in MMC patients) and in particular by the percentage of patients aged 80 or above (24.69% in PMC patients and 11.84% in MMC patients).

Our overall 5-year DFS was similar to the data from Bae et al. Between the two groups there were small, non-statistically significant differences ($p = 0.182$). This is another piece of data which supports the low percentage of local recurrence of this tumor: in fact we found only three cases of local recurrence in the MMC group (3.95%) and five cases in the PMC group (6.17%). The differences were not statistically significant ($p = 0.721$).

Regarding surgical treatment, breast conservative surgeries were the most used techniques (78.34% of all surgical treatments), especially in PMC patients (88.89% vs 67.11% of MMC patients). This is principally due to the greater tumor diameter at diagnosis in MMC patients (22.46 mm vs 18.75 mm of PMC patients) and it is also influenced by the age at diagnosis.

According to the published data, MMC has a greater capacity to metastasize to the lymph nodes. This was confirmed in our database: 43.42% of MMC patients underwent ALND (compared to 14.81% of PMC patients, $p < 0.001$) and in 31.58% we found axillary metastases (compared to 11.11% of PMC patients, $p < 0.001$). However, the mean number of metastatic lymph nodes did not differ greatly between the two groups (2.91 in MMC patients and 2.7 in PMC patients).

Regarding biological profiles, the low percentage of Her2-enriched and triple-negative tumors influenced oncologic treatment. In fact, only 6.37% of the patients underwent neoadjuvant treatment. In the two groups, we found significant differences regarding luminal-A and luminal-B patients: luminal-A tumors were more frequent in PMC patients (61.73% vs 35.53% in MMC patients, $p < 0.001$), while luminal-B tumors were more frequent in MMC patients (61.84% vs 38.27% in PMC patients, $p < 0.05$). This influenced the therapeutic decision: adjuvant chemotherapy was administered to 31.58% of MMC patients, but only 7.41% of PMC patients also received this treatment. On the other hand, both PMC and MMC patients received hormone treatment in most cases (88.89% in the PMC group and 81.58% in the MMC group).

Conclusion

Our data confirmed that published in the peer-reviewed medical literature, and moreover it showed major differences between PMC and MMC patients. These differences influence prognosis and treatment strategies. Unfortunately, as yet there are no tailored therapies for MMC and PMC tumors, but their clinical behaviour often leads to an effective treatment strategy.

Despite the low frequency of the disease, knowledge of this kind of tumor could led to even better survival rates in the future.

Appendices

Conflict of interests

The authors declare that they have no conflict of interest in relation to this work.

Declaration of interests

All contributing authors have no financial or personal relationships with other people or organizations that could inappropriately influence or bias the current work.

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Figure legends

Fig. 1. Overall Survival rate of PMC and MMC

Fig. 2. Disease Free Survival rate of PMC and MMC

Table

SUBTYPE	CHARACTERISTICS	
PMC	> 90% of mucinous components	
	PMC-A	Growth pattern: papillary, micropapillary, tubular, cord-like or cribriform
	PMC-B	Growth pattern: solid nests
MMC	30-90% of mucinous components	
	pMMC	30-50% of mucinous components
	mMMC	50-90% of mucinous components

Table 1 – Subtypes of Mucinous Breast cancer (MC)

Author	5-year DFS	5-year OS	No. of patients	Median FUP (months)
Di Saverio (2008)	NA	94%	11400	NA
Bae SY (2011)	95.2%	98.9%	268	49.7
Cao AY (2012)	85%	95%	309	43.3
Tseng (2013)	NA	94.5% (10years)	93	NA

Table 2 – Results of literature review

LEGEND: NA = Not Available

Table 3

	TOT	PMC	MMC	p
Number of patients	157	81	76	
Age at diagnosis (mean ± DS)	64.4 ± 15.2	69.1 ± 13.8	59.4 ± 15.0	**<0.001**
Patients aged 80 or over	18,47%	24,69%	11,84%	
Median follow-up (months)	35 (0 - 353)	29 (0 -145)	46 (0 -353)	
OS 5-year	92.07% (85.63% - 95.70%)	87.10% (75.39% - 93.47%)	96.84% (87.91% - 99.20%)	0.041
DFS 5-year	95.27% (88.83% - 98.04%)	94.05% (82.17% - 98.10%)	96.43% (86.31% - 99.11%)	0.182
Local recurrence (number)	8	5	3	
Local recurrence (%)	5.10%	6.17%	3.95%	0.721
SURGERY ON "T"	**TOT**	**PMC**	**MMC**	
BCS (num)	123	72	51	
BCS (%)	78.34%	88.89%	67.11%	**0.001**
Mastectomy (number)	34	9	25	
Mastectomy (%)	21.66%	11.11%	32.89%	**0.001**
Tumor diameter (mm)	20.55 ± 16.88	18.75 ± 11.88	22.46 ± 20.85	0.691
SURGERY ON "N"	**TOT**	**PMC**	**MMC**	
SLNB (number)	107	55	52	
SLNB (%)	68.15%	67.90%	68.42%	0.944
ALND (number)	45	12	33	
ALND (%)	28.66%	14.81%	43.42%	**<0.001**
No axillary surgery (number)	27	18	9	
No axillary surgery (%)	17.20%	22.22%	11.84%	0.095
Lymph node metastases (number)	33	9	24	
Lymph node metastases (%)	21.02%	11.11%	31.58%	
Number of examined lymph nodes (mean + range)	16.97 (1-31)	16.7 (1-27)	15.67 (1-31)	
Number of metastatic lymph nodes (mean + range)	2.80 (1-31)	2.7 (1-10)	2.91 (1-14)	
OTHER TREATMENTS	**TOT**	**PMC**	**MMC**	
Adjuvant chemotherapy (n)	30	6	24	
Adjuvant chemotherapy (%)	19.11%	7.41%	31.58%	**<0.001**
Neoadjuvant chemotherapy (n)	10	4	6	
Neoadjuvant chemotherapy (%)	6.37%	4.94%	7.89%	0.525
Adjuvant hormone therapy (n)	134	72.00	62.00	
Adjuvant hormone therapy (%)	85.35%	88.89%	81.58%	
Adjuvant radiotherapy (n)	132	68	64	
Adjuvant radiotherapy (%)	84.08%	83.95%	84.21%	0.891
BIOLOGICAL PROFILE	**TOT**	**PMC**	**MMC**	
Luminal A-like (n)	77	50	27	
Luminal A (%)	49.04%	61.73%	35.53%	**0.001**
Luminal B-like (n)	78	31	47	

Luminal B (%)	49.68%	38.27%	61.84%	**0.004**
Her2-enriched (n)	1	0	1	
Her2-enriched (%)	0.64%	0.00%	1.32%	0.484
Triple-negative (n)	1	0	1	
Triple-negative (%)	0.64%	0.00%	1.32%	0.484

Table 3 – Clinicopathological characteristics of Pure Mucinous Carcinoma (PMC) and Mixed Mucinous Carcinoma (MMC) treated in Humanitas Research Hospital between 2008 and 2018

Figure 1

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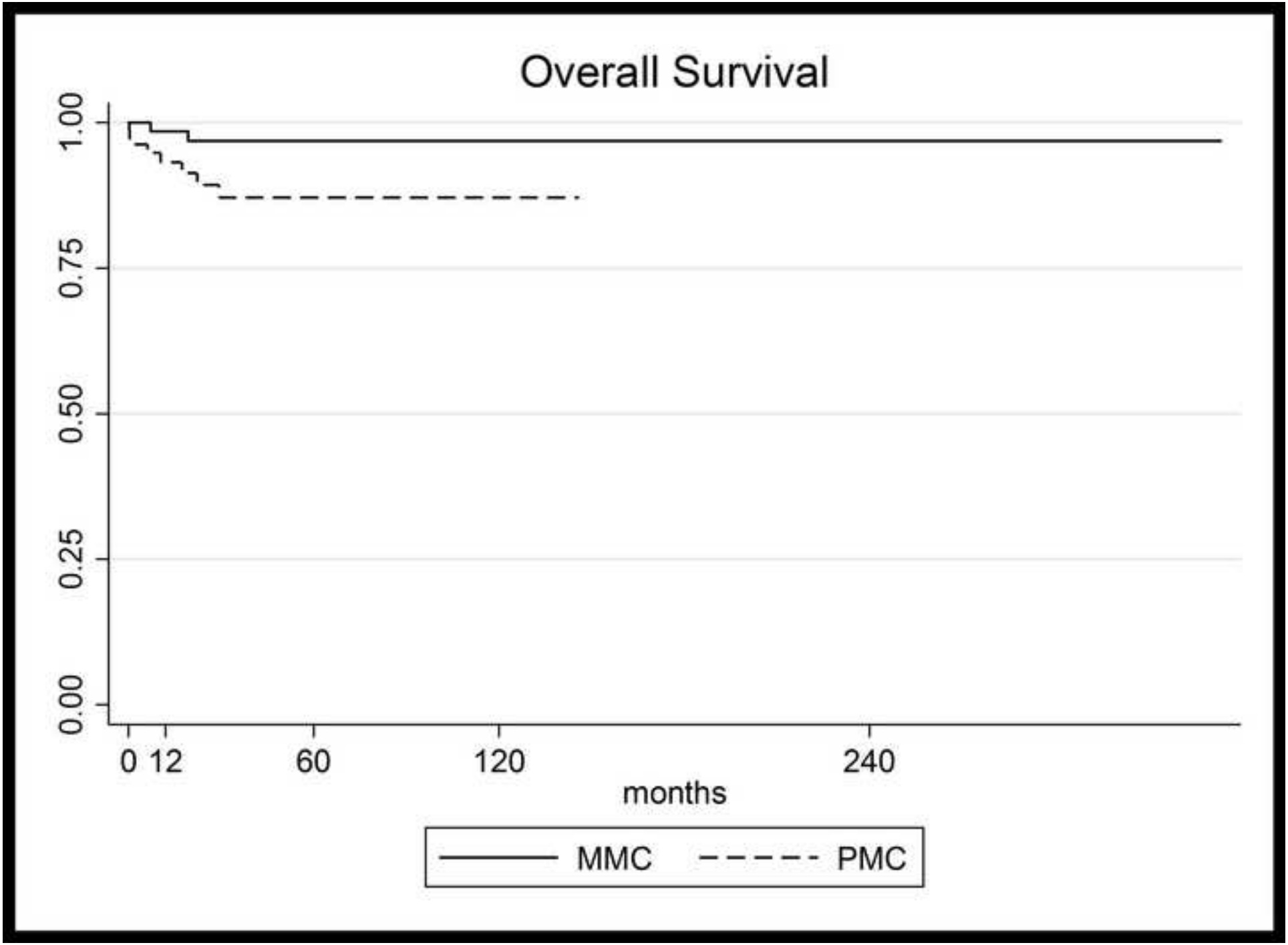

Figure 2

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