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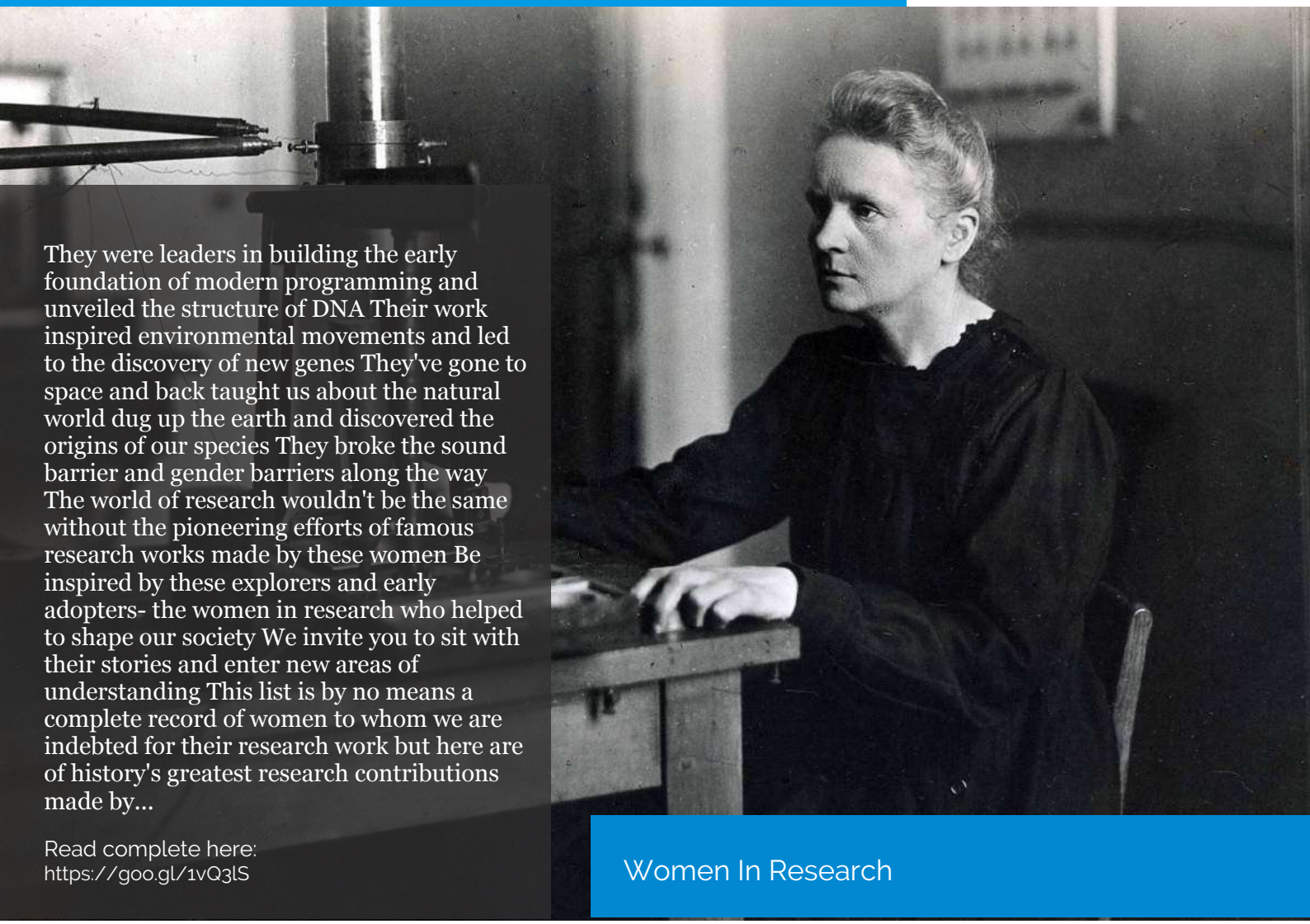

They were leaders in building the early foundation of modern programming and unveiled the structure of DNA Their work inspired environmental movements and led to the discovery of new genes They've gone to space and back taught us about the natural world dug up the earth and discovered the origins of our species They broke the sound barrier and gender barriers along the way The world of research wouldn't be the same without the pioneering efforts of famous research works made by these women Be inspired by these explorers and early adopters- the women in research who helped to shape our society We invite you to sit with their stories and enter new areas of understanding This list is by no means a complete record of women to whom we are indebted for their research work but here are of history's greatest research contributions made by...

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Ming C. Liau, Christine L. Craig & Linda L. Baker

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Keywords: CCs; CSCs; cancer therapy; DIs; DHIs; differentiation therapy; wound healing.

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Wound healing requires the proliferation and the terminal differentiation of progenitor stem cells (PSCs), which are the most primitive stem cells to give rise to the particular organ or tissue during the development of the fetus. Methylation enzymes(MEs) of PSCs are abnormal due to the association with telomerase. MEs play a pivotal role on the regulation of cell replication and differentiation. Because of this pivotal role, MEs are subject to exceptional double allosteric regulations: one on the individual enzymes and one on the enzyme complex. The association of telomerase with the enzyme complex of MEs tilts the regulation greatly in favor of cell growth, which is apparently very important for the development of fetus and the wound healing. Efficient destabilization of abnormal MEs is a critical process of wound healing. The nature creates chemo-surveillance as an allosteric regulation to ensure perfection of wound healing. Human body produces metabolites active as differentiation inducers (DIs) and differentiation helper inducers (DHIs) to keep a check on abnormal MEs. Healthy people can maintain a steady level of cell differentiation agent (CDA), which is a term to designate DIs and DHIs, to ensure perfection of wound healing to avoid disastrous consequences of wound unhealing that can be tissue fibrosis, dementia, organ failure and cancer. Wound healing is a simple matter that comes naturally. Solution of cancer should also be a simple matter as wound healing if the therapy is done right. CDA formulations are the right solution of cancer, which are preparations made up by DIs and DHIs that can direct differentiation of cancer stem cells (CSCs) and CCs, and to restore chemo-surveillance to save cancer patients.

Keywords: CCs; CSCs; cancer therapy; DIs; DHIs; differentiation therapy; wound healing.

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I. INTRODUCTION

Cancer is a fearful disease, because cancer establishments do not handle it right to let cancer mortality remains at historic high. According to NCI experts, the cancer incidence was 19 million and the cancer mortality was 10 million worldwide in 2019, which were on the way to increase at an annual increment of 5% [1]. President Biden in 2022 called for the reduction of cancer mortality by 2% annually to reach 50% reduction in 25 years [2]. Health profession must get serious to develop alternatives than those they have been relying on in the past to reduce cancer mortality. Cancer therapy got to a bad start to rely on toxic chemicals to combat cancer. Cytotoxic

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chemotherapy was a tragic byproduct of World War II. During the war, toxic sulfur mustard gas bombs were used. Victims of toxic gas all showed depletion of lymphocytes in their blood specimens, which inspired oncologists to employ toxic chemicals to treat leukemia patients.

Cytotoxic chemotherapy was thus established as the standard care of cancer, and the disappearance of cancer cells or the tumor was the exclusive criterion for the judgement of therapeutic efficacy. Both the selection of toxic agents and the disappearance of tumor for the evaluation of therapeutic efficacy were serious mistakes of cancer establishments to contribute the horrendous cancer mortality [3-5]. Cancer establishments were given ample opportunities including a presidential project of war on cancer during 1971-1976 to solve cancer, but they failed the challenges. The failure is attributable to the wrong approach relying on the killing of CCs [6].

Cancer is caused by wound unhealing due to the collapse of chemo-surveillance. Creating more wounds by cytotoxic agents contribute to the destruction of chemo-surveillance, clearly is contra-indication of therapy [7, 8]. This adverse effect and the ineffectiveness of cytotoxic agents against cancer stem cells (CSCs) contribute to the failure of this strategy to win the war on cancer.

CSCs are protected by drug resistance and anti-apoptosis mechanisms to resist cytotoxic agents [9]. Cytotoxic agents can only benefit a minority of early stage cancer patients whose chemo-surveillance has not yet been fatally damaged, relying on the recovery of chemo-surveillance to subdue surviving CSCs, whereas a majority of advanced cancer patients whose chemo-surveillance has been fatally damaged are either wiped out as unresponsive cancer patients, or even lucky enough to reach complete remission are eventually succumbed to recurrence [4, 5]. A drastic change of cancer establishments is necessary to save cancer patients [10]. Cancer evolves as a consequence of wound not healing properly [8]. The best strategy to save cancer patients is to follow the wound healing process [7, 11].

II. COMMENTARIES AND DISCUSSION

2.1 Failure of Cytotoxic Agents to Save Advanced Cancer Patients

Cancer is a very fearful disease, because the approved treatments are so excruciating, and the mortality is so high. This is all because of the mishandlings of cancer establishments. Cancer therapy got to a bad start. The use of toxic agents to stop fast growing CCs was acceptable at a time when we did not have full knowledge of cancer. After all, cytotoxic agents were very effective to kill CCs, the most outstanding symptom of cancer.

Cytotoxic drugs and radiation were the major drugs used in the combat of cancer during the war on cancer declared by President Nixon, but failed to achieve the goal [12]. If a treatment modality has been drilled through as a presidential project and failed, it was fair to conclude that the modality employed was not good for cancer therapy. Now we have better knowledge of cancer, and cancer establishments are still relying on these failed drugs to treat cancer patients, that is irresponsible. Cytotoxic agents can only benefit a small minority of early stage patients, but contribute to the deaths of a majority of advanced cancer patients [3-5]. President Biden lost his very accomplished son, congressman Beau, to malignant brain tumor. He was genuinely concerned with high cancer mortality. It is time for health profession to get serious to remove cytotoxic agents contributing to cancer mortality, particularly DNA reacting agents such as nucleoside analogs, platinum derivatives, intercalating agents, apoptosis inducing agents and radiation. It is also advisable to remove the use of the reduction of tumor size as a criterion for the evaluation of cancer drugs, which is a darn mistake of cancer establishments to allow only cytotoxic agents that cannot put cancer away and to block the development of good cancer drugs not based on the killing of CCs. The development of good cancer drugs is essential to save unresponsive cancer patients attributable to cytotoxic agents [4, 5, 13]. Cancer establishments are the bosses. The health professionals can do nothing. Perhaps President Jimmy Carter as a victim of toxic cancer drugs can lodge a protest and plead for the approval of good cancer drugs

such as CDA formulations that can eliminate CSCs to come to the rescue of a lot of terminal cancer patients in the desperate situation as himself [13, 14].

2.2 Cancer Evolves as a Consequence of Wound Unhealing

The concept of cancer as wound unhealing was first introduced by the great German scientist Virchow in the 19th century [15]. It was again brought up by Dvorak in 1986 [16]. The close relationship between cancer and wound healing was noticed by MacCarthy-Morrough and Martin [17]. We provided the most important details on this subject that included abnormal MEs to block differentiation [18-20]; chemo-surveillance as the nature's creation of allosteric regulation to ensure perfection of wound healing [5, 21-23]; DIs, which are metabolites capable of eliminating telomerase from abnormal MEs, and DHIs, which are metabolites capable of inhibition of MEs, as wound healing metabolites and as the active players of chemo-surveillance [5, 21-23]; hypomethylation of nucleic acids as the most critical mechanism for the induction of terminal differentiation of cells with abnormal MEs [24]; the mechanism of wound healing to involve the proliferation and the terminal differentiation of PSCs [25-27]; and the evolution of CSCs from PSCs due to wound unhealing [9, 28, 29]. Studies above described are very convincing that cancer is caused due to the failure of wound healing.

Our carcinogenesis studies strongly supported the validity of these findings. During the challenge with hepatocarcinogen, numerous tiny hyperplastic nodules appeared before the appearance of large size carcinoma, which displayed abnormal MEs [30]. These hyperplastic nodules must represent proliferation of PSCs in the process of active repair. Most of these hyperplastic nodules disappeared, indicating completion of wound healing, and only a few large size carcinomas appeared later, which must be derived from the tiny hyperplastic nodules failed to heal. If Antineoplaston A10 was provided during the challenge with hepatocarcinogen, development of carcinomas could be prevented [31]. Antineoplaston A10 is phenylacetylglutamine which is an effective anti-cachexia agent to protect the integrity of chemo-surveillance [21]. Our carcinogenesis studies strongly support the evolution of cancer due to wound unhealing. Then the right approach of cancer therapy should employ pro-wound healing strategy. A right approach is essential to the success to put away any challenge, including illness. Cytotoxic agents create more wounds that is a wrong approach of cancer therapy. A wrong approach cannot solve anything even a very simple matter. By employing a wrong approach of anti-wound healing therapy, cancer establishments turn a simple wound unhealing problem to become an unsolvable problem.

2.3 Mechanism of Wound Healing

Wound healing comes naturally. So, nobody cares how wound is healed. Take surgical wound for example, suture and antibiotics are subsidiary to speed up the wound healing and to prevent infections that may interfere with wound healing. The treatments have nothing to do with wound healing. Wound healing requires the proliferation and the terminal differentiation of PSCs. PSCs are the most primitive pluripotent stem cells to give rise to organ or tissue during the embryonic development of the fetus. A small amount of these cells, usually less than 2% of the mass, are reserved in the organ or tissue for future expansion or repair. Wound triggers biological and immunological responses. The biological response involves the release of arachidonic acid (AA) from membrane bound phosphatidylinositol for the synthesis of prostaglandins (PGs), which are important for wound healing [32] to trigger edema for the extravasation of inhibitors such as DIs and DHIs for PSCs to proliferate. Since PGs are unstable metabolites, the final act of terminal differentiation of PSCs must be achieved by chemo-surveillance functioning as allosteric regulators to destabilize abnormal MEs. Therefore, we believe the synthesis of PGs is to facilitate the proliferation of PSCs, and the final act of wound healing is the terminal differentiation of PSCs to give rise to damaged components, which is the most critical mechanism of wound healing [24]. Terminal differentiation of PSCs depends on the integrity of

chemo-surveillance [5, 21-23]. If the chemo-surveillance is functioning perfectly, wound healing comes naturally. If the chemo-surveillance is not functioning perfectly, then the troubles may ensue, that can be tissue fibrosis, dementia, organ failure and cancer. The nature creates chemo-surveillance to prevent such disastrous consequences from happening.

Wound healing is an important health issue, so that the nature creates chemo-surveillance to ensure perfection of wound healing. Chemo-surveillance was a term we created to describe a natural defense mechanism against cancer, which was based on the observation that healthy people could maintain a steady level of metabolites active as DIs and DHIs, whereas cancer patients tended to show deficiency of such metabolites [21]. We have identified acidic peptides, AA, membrane fragments containing AA as the major DIs [33-37], and uroerythrin, pregnenolone, steroid metabolites, amino acid derivatives and fatty acid derivatives as the major DHIs [35, 38-41]. Active DIs and DHIs are degradative products of erythrocytes and metabolites of organs involved in steroid metabolism. Healthy people can maintain a steady level of DIs and DHIs. The steady level of DIs and DHIs may be disrupted under pathological conditions which trigger the production of TNF to display cachexia symptom. A manifestation of cachexia symptom is excessive urinary excretion of low molecular weight metabolites due to membrane hyperpermeability caused by TNF [42, 43]. DIs and DHIs are among low molecular weight metabolites excreted. In general, pathological conditions resulting from wound, toxic chemicals, infections and inflammatory responses are at a risk of causing damage to chemo-surveillance. The collapse of chemo-surveillance is a contributing factor of wound unhealing. The host will respond by forcing PSCs to proliferate. The contact inhibition prohibits the proliferation of PSCs beyond the damaged space. The pressure will be put on PSCs to evolve into CSCs to escape contact inhibition. It takes a single hit to silence TET-1 enzyme to turn PSCs into CSCs that is within the reach of PSCs equipped with abnormally active MEs. The problem of wound unhealing is due to the collapse of chemo-surveillance. The proliferation of CSCs still cannot heal the wound. More pressure will set in to force slow growing CSCs to progress to faster growing CCs by chromosomal translocations to activate oncogenes, or deletions to inactivate suppressor genes. The build up of PSCs unable to undergo terminal differentiation is the cause of tissue fibrosis, such as white lung due to COVID-19 infection, or hepatic cirrhosis due to hepatitis. Dementia is caused by toxic peptide amyloid beta, analogous to TNF to result in wound unhealing. For the therapy of tissue fibrosis, application of suitable amount of phenylacetylglutamine, which is an effective anti-cachexia chemical [21], and a preparation of CDA-CSC made up by ED_{50} of AA and $2xRI_{0.5}$ pregnenolone [11, 13, 35] can be very effective. Dementia is a tough medical problem as difficult as cancer. More studies will be needed to come up a good solution. For the therapy of cancer, an additional CDA-CC made up by ED_{50} of BIBR1532 and $2xRI_{0.5}$ of pyrvinium pamoate [11, 13, 35] may be needed to provide a satisfactory result. Natural DIs and DHIs are good for the therapy of PSCs and CSCs since they are the partners of PSCs and CSCs to carry out wound healing. PSCs and CSCs are protected by drug resistance mechanism, non-natural chemicals may be rejected. Fast growing CCs are known to express a high level of degradative enzymes to salvage natural metabolites as the substrates for macromolecular syntheses in order to support their faster growth. Natural metabolites may be rapidly degraded to lose biological activities. Non-natural drugs are a better choice for the therapy of CCs.

2.4 Restoration of Chemo-surveillance as a Top Priority to Save Cancer Patients

DIs and DHIs are wound healing metabolites and are also the active players of chemo-surveillance. Cancer evolves as a consequence of the collapse of chemo-surveillance. DIs and DHIs are hydrophobic metabolites that can be retained by C18 and eluted from C18 with 80% methanol. Acidic peptides are very active DIs. Not all peptides are active as DIs. But peptides share physical-chemical properties similar to most active DIs and DHIs. Therefore, peptides can be used as surrogate molecules to represent CDA, a

term to designate DIs and DHIs, levels of plasma and urine. We have carried out quantitative analyses of plasma and urinary peptides of healthy people and cancer patients by initial peptide purification through C18 cartridge as above described, and then resolved peptide profile through HPLC on a column of sulfonated polystyrene and ninhydrin reaction. Quantitative data were computed by integrator. As presented in Table 1, Only 2% of cancer patients showed CDA level as high as 5.0 as the healthy people, and only 25% of cancer patients showed CDA levels above 3.0. We assume CDA 3 is a critical level to account for the responsiveness to cytotoxic therapy. Above CDA3, patients may have chance to be cured. Below CDA3 patients may not have chance to be cured. But if the therapy is carried out by CDA formulations, all patients can respond positively to a full recovery. Evidently, the progression of cancer drives CDA levels to decline, since cancer growth and inflammatory conditions contribute to cachexia symptom to cause the decline of CDA levels. Therapy with cytotoxic agents accelerates the decline of CDA levels. We believe boosting CDA levels can benefit cancer therapy, even the therapy is carried out with cytotoxic agents [5]. CDA -2 was a preparation of wound healing metabolites purified from freshly collected urine [44], which was approved for cancer therapy by the Chinese FDA based on its ability to boost CDA levels to enhance therapeutic efficacy of cytotoxic chemotherapy and to greatly improve quality of life of cancer patients [45]. CDA-2 is a drug effective to eliminate CSCs by induction of terminal differentiation, the critical mechanism of wound healing. The ability to eliminate CSCs is an absolute requirement of good cancer drugs.

Table 1: Plasma/Urine Peptide Ratios of Cancer Patients

Plasma/Urine	CDA Peptide Ratios	No. of Patients Levels	% Distribution
0.8 - 0.83	5.0	2 (Normal)	1.8
0.6 - 0.8	4.3	7	6.5
0.4 - 0.6	3.1	18	16.7
0.2 - 0.4	1.8	38	35.2
0.1 - 0.2	0.9	24	22.2
0.02 - 0.1	0.4	19	17.6

Plasma Peptides: nmoles/ml; Urine Peptides: nmoles/mg creatinine

2.5 Abnormal MEs as the Most Critical Issue of Cancer

Perpetual proliferation of CCs is the most outstanding feature of cancer. Abnormal MEs and the collapse of chemo-surveillance resulting in the blockade of differentiation is an important factor.

Another important factor is the activation of oncogenes or the inactivation of suppressor genes. Abnormal MEs is due to the association of telomerase with MEs [20], that happens on PSCs, the precursors of CSCs, and passes on to CSCs and then to CCs. This abnormality is universal to all cancers [19]. The activation of oncogenes or the inactivation of suppressor genes happens quite late during the evolution of cancer. The abnormalities are variable among different cancers. A solution of abnormal MEs is applicable to all cancers. Once abnormal MEs is solved, the solution can also put to rest chromosomal abnormalities which are otherwise very difficult to solve. Oncogenes and suppressor genes are cell cycle regulatory genes, which have very important roles to play when cells are in cell cycle replicating. If the replicating cell is diverted to undergo terminal differentiation through destabilization of abnormal MEs to exit cell cycle, then abnormal chromosomal abnormalities have no roles to play. Chromosomal abnormalities are variable and the solution is extremely difficult. Even a difficult chromosomal abnormality is solved, there may soon pop up another chromosomal abnormality. Development of unresponsiveness is a frequent problem of

targeted therapy. It is an endless efforts trying to put away all chromosomal abnormalities. Even all chromosomal abnormalities can be put away, the problem of abnormal MEs remains unsolved. We considered abnormal MEs as the most critical issue of cancer [46], which are the bullseye for targeted therapy [47]. If the problem of abnormal MEs is fixed by CDA formulaions, the remission can last life time. Remission achieved by cytotoxic agents frequently recurs in a short while.

MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT) methyl-transferase (MT) - S-adenosylhomocysteine hydrolase (SAHH) [48]. MEs maintain enzyme complex on gel filtration and sucrose density sedimentation, but dissociate into individual enzymes upon DEAE-agarose chromatography. Individual enzymes display sedimentation values as 4S for SAHH, 5.5S for MT and 6S for MAT.

SAHH is a steroid hormone receptor, which is the most unstable enzyme of the three, requiring steroid hormone or related molecules to assume stable configuration to form dimeric enzyme complex with MT, MT-SAHH dimer displays a sedimentation of 6S similar to that of MAT. A ternary enzyme complex is formed between MAT and MT-SAHH dimer. Thus, MEs are under the allosteric regulation of steroid hormone to form stable and active ternary enzyme complex and become inactive as dissociated individual enzymes in the absence of allosteric regulators. MTs in the individual enzyme state have the tendency to be modified to become nucleases which can trigger apoptosis to cause organ involution.

MEs play a pivotal role on the regulation of cell replication and differentiation by virtue of the fact that DNA methylation controls the expression of tissue specific genes [49], and pre-rRNA methylation controls the production of ribosome [50], which in turn dictates the commitment of cell to initiate cell replication [51]. If enhanced production of ribosome is locked in place, it becomes a factor to drive carcinogenesis [52].

Because of such pivotal role, MEs are subject to exceptional double allosteric regulations: one on the individual enzymes and one on the enzyme complex. On the individual enzymes, SAHH is allosteric regulated by steroid hormones or related allosterically regulators as above described. In telomerase expressing cells, MEs become associated with telomerase [20]. The association with telomerase changes kinetic properties of MEs and the regulation to tilt in favor of growth. K_m values of the telomerase associated MAT-SAHH isozyme pair are 7-fold higher than the normal isozyme pair. The increased K_m values suggest that telomerase expressing cells have much larger pool sizes of S-adenosylmethionine (AdoMet) and S-adenosylhomocysteine (AdoHcy). A larger pool sizes of AdoMet and AdoHcy is important for the build up of cells with abnormal MEs to conduct their biological functions. It has been shown by Prudova et al. [53] that AdoMet could protect protein from protease digestion. Chiba et al. [54] found that pool sizes of AdoMet and AcoHcy shrunk greatly when HL-60 cells were induced to undergo terminal differentiation. Obviously, abnormal MEs play an important role for the build up of cells with abnormal MEs. The build up of normal stem cells with abnormal MEs such as embryonic stem cells and PSCs is important for the development of the fetus or for wound healing. MEs turn abnormal do not seem to create problems for normal primitive cells, because there are mechanisms to limit the build up to become problematic, mechanisms such as contact inhibition, TET-1 enzyme to direct lineage transitions, and chemo-surveillance to keep a check on abnormal MEs. Problems arise when these safety mechanisms become dysfunctional [21, 23, 25-27, 55, 56]. Restoring the safety mechanisms on abnormal MEs is obviously the best strategy to save cancer patients.

2.6 Screening of Good Cancer Drugs via MDS

MDS are diseases to display the evolution of CSCs from PSCs by a single hit to silence TET-1 enzyme to allow building up of CSCs unable to undergo terminal differentiation. They are a typical case of intermediary cancer, namely cancer at the stage of CSCs.

MDS often start with a display of an immunological disorder [57], which prompts the production of immunological cytokines. Among

such cytokines, TNF is the most critical factor related to the development of MDS [58]. It causes excessive apoptosis of bone marrow stem cells, thus severely affecting the ability of the patient to produce hematopoietic cells such as erythrocytes, platelets and neutrophils. TNF is also named cachectin after its effect to cause cachexia which is responsible for the collapse of chemo-surveillance to result in the evolution of CSCs from PSCs. The propagating cells of MDS have been identified as human CSCs [59]. So, MDS are diseases due to wounds triggering immunological disorder which are not healed to result in the evolution of PSCs to become CSCs. The therapy of MDS is obviously to turn CSCs to functional erythrocytes, platelets and neutrophils, that requires the critical mechanism of wound healing to efficiently promote terminal differentiation of PSCs and CSCs. The killing of CSCs, which is the choice of cancer establishments, cannot cure MDS. Besides, killing of CSCs is a task that cannot be easily done. So far, Vidaza, Decitabine and CDA-2 are the three drugs approved for the therapy of MDS. Professor Jun Ma, Director of Harbin Institute of Hematology and Oncology, was instrumental to conduct clinical trials of these three drugs for the Chinese FDA to approve. Vidaza and Decitabine were also approved by the US FDA. According to Professor Ma, based on two cycles of treatment protocols, CDA-2 had a slightly better efficacy based on cytological evaluation, and a markedly better efficacy based on hematological improvement efficacy, namely no longer dependent on blood transfusion to stay heathy, as shown in Figure 1 [60]. The therapy of MDS by these three drugs is based on the inactivation of abnormal MEs, CDA-2 by the elimination of telomerase from abnormal MEs, and Vidaza and Decitabine by inducing covalent bond formation between methyltransferase and 5-azacytosine incorporated into DNA [61]. CDA-2 exercises a selective action on cancer MEs, whereas Vidaza and Decitabine titrate out MEs non-selectively. Adverse effects of Vidaza and Decitabine include induction of cancer [62, 63], and toxicities to DNA [64-66]. CDA-2 is devoid of serious adverse effects. Drugs effective against MDS are good cancer drugs that can induce CSCs to undergo terminal differentiation

Drugs ineffective against CSCs are bad cancer drugs. MDS can be used to screen good cancer drugs. Evidently, CDA-2 is a perfect good cancer drug. Vidaza and Decitabine are imperfect good cancer drugs because of toxicities as nucleoside analogs.

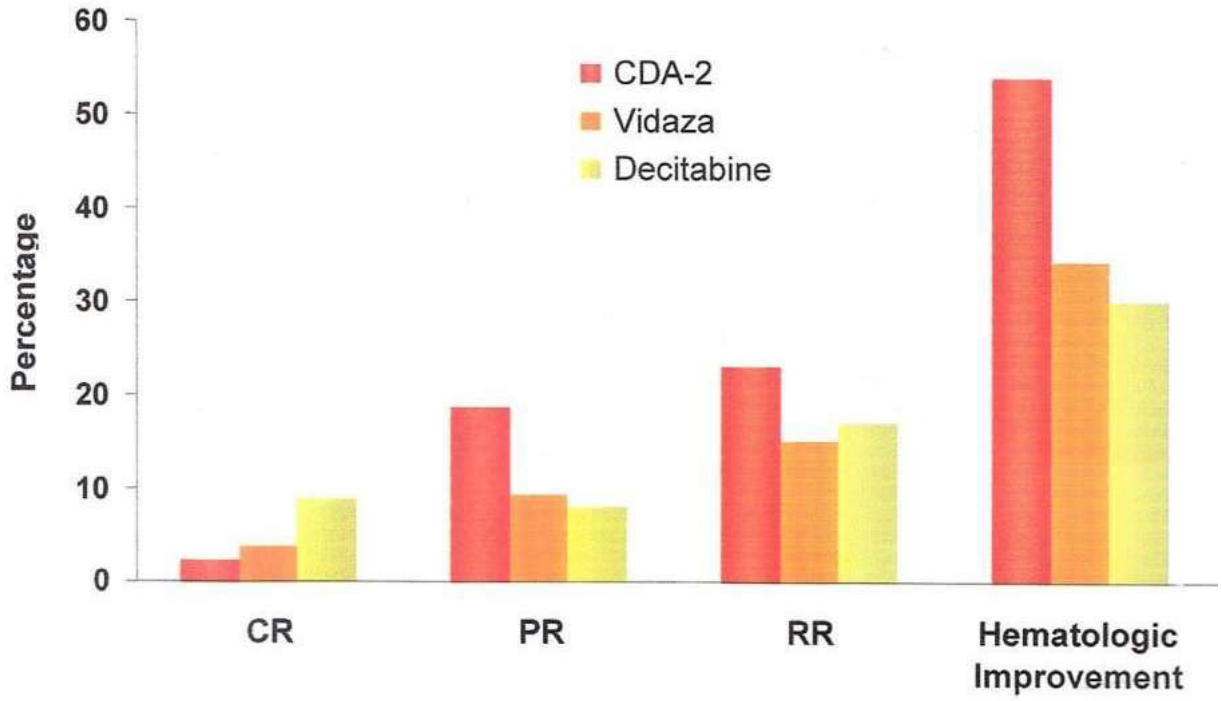

Figure 1: A Comparison of Therapeutic Efficacy of CDA-2, Vidaza and Decitabine on MDS

III. CONCLUSION

A good cancer drug must be able to take out both CSCs and CCs, and to restore chemo-surveillance. MDS are diseases attributable entirely to the propagation of CSCs, which are ideal for the screening of good cancer drugs. Only drugs able to inactivate abnormal MEs can offer therapeutic effects on MDS. CDA formulations are the best choice as good cancer drugs.

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ABSTRACT

Background: Breast Cancer (BC) is the main cause of death and disability among women in low- and middle-income (MIC) countries like Argentina. In BC the study of genic profile of cancer has been encouraged. Implementation of the multigene panels assay has led to a change in the manner in which chemotherapy is utilized mainly in patients with, early stage, estrogen receptor (ER)-positive, Her2-neu negative, lymph node-negative BC. Unfortunately, all these tests are expensive. Given the potential savings in cost, algorithms have been proposed to predict Oncotype DX recurrence score (ODX RS) using commonly acquired clinical and histopathologic variables designated as subrogate parameters (SP).

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Background: Breast Cancer (BC) is the main cause of death and disability among women in low- and middle-income (MIC) countries like Argentina. In BC the study of genic profile of cancer has been encouraged. Implementation of the multigene panels assay has led to a change in the manner in which chemotherapy is utilized mainly in patients with, early stage, estrogen receptor (ER)-positive, Her2-neu negative, lymph node-negative BC. Unfortunately, all these tests are expensive. Given the potential savings in cost, algorithms have been proposed to predict Oncotype DX recurrence score (ODX RS) using commonly acquired clinical and histopathologic variables designated as subrogate parameters (SP).

Materials and Methods: We evaluate the possibility, in a MIC country, of having the necessary data from the normally required report of the BC, in order to apply some of the ten (10) selected published algorithms offered as alternatives to ODXRS. From 1832 (stage I to IV) BC cases reported, between 2012 and 2015, a subset of 706 (38,5%) early stages "ER (+) / HER2 (-) / lymph node-negative" BC, was identified and analyzed. An online search and selection of published scientific research on same thematic, from 2010 onwards, was carried out. The selected 10 publications were analyzed and the SP used in them identified. The presence of the SP shared by the different studies was analyzed in our series, namely: age, tumor size, histology, grade, Estrogen/Progesterone receptor, Her2 / neu status and Ki-67.

Results: From the total of 10 nomograms selected only in five our series can complete the required two SPs (HR/HER2) with percentages over 90% In the five remaining nomograms evaluated the percentage of cases that could complete the required SPs only reached 61.5% of the cases. Conclusion. We demonstrate that, although there are gaps in our country in the updated care process of BC, it is possible to use nomograms in through a comprehensive and complete collection and subsequent analysis of the conventional parameters normally present in the routine diagnosis of BC with special emphasis on the histopathological and immunohistochemical results, available almost routinely in our series.

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I. BACKGROUND

Breast Cancer (BC) is the most commonly diagnosed cancer amongst women worldwide [1] and is a leading cause of death and disability among women in low- and middle-income countries (MICs) among which is Argentina [2].

Nowadays in BC, beyond the standard determination of cancer stage according to the classic anatomical criteria of the TNM classification, expression of estrogen and progesterone receptors and HER2/neu receptor

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are required. The study of genic profile (GP) of cancer has also been encouraged although, for now, not in mandatory form [3] Implementation of the multigene panels assay has led to a change in the manner in which chemotherapy is utilized mainly in patients with, early stage, *estrogen receptor (ER)-positive, Her2-neu negative, lymph node-negative* [*ER (+) / HER2 (-) / lymph node-negative*], BC ensuring that patients at highest risk of recurrence are prescribed systemic treatment, while at the same time sparing low-risk patients potential adverse events from therapy unlikely to influence their survival [4,5].

Multigene panels can provide better risk discrimination relative to clinic-pathological factors, which are significantly superior to traditional prognostic factors in predicting clinical outcome and identifying patients who can be spared chemotherapy safely. There are several tests available at the moment. The Oncotype DX (ODX) BC recurrence test (ODXRS) is the one recommended based on the experience accumulated since its implementation in 2010 [6].

Unfortunately, all these tests are expensive. Oncotype DX (ODX) is expensive and is performed in only 1/3 of patients with BC positive for the estrogen receptor (ER) in developed countries [7,8] and are not affordable or available for the majority of the breast cancer patients globally [9]. The economic non-accessibility and / or technical availability are also the main reasons why in a middle-income country (MIC), such as Argentina, the study is only carried out in very few cases (0,23%) who fulfilled the established guidelines for gene-expression profile study and in a sporadic way [10].

Given the potential savings in cost and resource utilization, several algorithms have been proposed to predict Oncotype DX recurrence score (ODX RS) using commonly acquired clinical and histopathologic variables designated as subrogate parameters (SP). These studies reached different conclusions regarding which model demonstrated the best statistical discrimination power, mainly due to differences in clinical and pathologic variables used [11-20].

In this study we evaluate the possibility, in a MIC country such as Argentina, of having the necessary data from the normally required clinical-pathological report of the BC, in order to apply some selected published algorithms that are offered as alternatives to ODX to predict the ODX RS specifically in patients with "*ER (+) / HER2 (-) / negative lymph node* " cases.

II. MATERIALS AND METHODS

2.1 Data Source

We retrospectively reviewed the pathology reports from successive incident BC cases reported, between 2012 and 2014, to PROYCAM2012 *(www.cancerdemama2012.org.ar)* a consortium (still in force) created for the study of BC in Argentina [10]. The PROYCAM2012 recruited a total of 1832 (stage I to IV) BC until the end of the period under study. From the total of cases reported a subset of 706 (38,5%) *"ER (+) / HER2 (-) / lymph node-negative"* BC, was identified and analyzed.

2.2 Surrogate Parameters

An online search and selection of published scientific research on the same thematic from 2010 onwards, was carried out [11-20]. The presence of the SP shared by the different studies selected was analyzed in our series, namely: age, tumor size, histology, grade, Estrogen/ Progesterone receptor, Her2 / neu status and Ki-67.

III. RESULTS

3.1 Substitute Parameters in Selected Publications

The selected 10 publications were analyzed and the SP used in them identified as shown in table 1.

Table 1: Publications on Surrogate Parameters Published and Selected. Characteristics of the Selected Series

Reference	Breast cancer cases (n, %) ER(+; HER2 (-);lymph node-negative/Total	Notification period (years) Country	Clinical and pathologic markers required as SP
Auerbach J et al., 2010 [11]	138 cases with available Oncotype DX recurrence scores	USA	Tumor size, patient age, laterality, ER receptor, PR receptor results and HER2/neu result
Dellapasqua S et al. 2012 [12]	378/1063 (35,5%)	1990-1999 Australia, Canada, Hungary, Italy, New Zealand, Slovenia, South Africa, Spain, Sweden, and Switzerland.	Age, Histotype, Tumor size, Grade, ER/PgR , Her2/neu status and Ki-67.
Rouanet R et al.,2013 [13]	714/1271 (56,1%)	1994-2004 France	HR and HER2 status. HER2-HR+; HER2-HR-; HER2+HR+; HER2+HR-
Turner B et al; 2015 [14]	299 cases with available Oncotype DX recurrence scores	2009-2013 USA	ER, PR, HER-2, and Ki-67, Nottingham score (NS) and tumor size.
Gage MM et al.2015 [15]	221ODX-tested ER(+)/HER2(-)/lymph node-negative	2006–2013 USA.	-Low grade and positive progesterone receptor tumors (LG+PR). -High grade or low estrogen receptor (ER) (ER < 20%) tumors (HG/ LER).
Özmen V et al., 2016 [16]	165 ODX-tested ER(+)/HER2(-) /lymph node-negative	Turkey	Age, LN Status, Grade, ER score ≤10%, PR score ≤20% and Ki67 score.
Harowicz MR et al., 2017 [17]	305 ODX-tested ER (+) /HER2(-)/lymph node-negative	2000-2014 USA	Estrogen receptor status and progesterone receptor status along with different combinations of grade, proliferation indices (Ki-67, mitotic rate), HER2 status, and tumor size.
Farrugia DJ et al,2017 [17]	237/614 (38,5%)	2010-2014 USA	Magee Equation 3 test: ER, PR, HER2 status and Ki-67.
Hanna MG et al.2017 [19]	536 ODX-tested ER (+)/ lymph node-negative	2007-2013 USA	Size, ER, PR status, HER2neu, Nottingham and histomorpho-logy.
Orucevic et al,2019.[20]	65,754 ODX-tested ER (+) / HER2 (-)/lymph node-negative	2010-2014 USA	Age, tumour size, grade, PR status and histologic type.

3.2 Clinical-Pathological Characteristics

The subset of 706 (38,5%) "*ER (+) / HER2 (-) / lymph node-negative" cases* selected from a database of 1832 cases of BC (stages I-IV) showed the following clinic-pathological characteristics (Table 2). The main clinical characteristics that define this group are: predominant in menopausal women (72%), average age of 61 years, 3.2% bilaterally and a personal (30,3%) and/or family history (9,3%) of BC. Pathologically, the average size of the tumors is between 1.8 -2.0, cm according to the left and right side, with predominance of infiltrating ductal lesions (67, 7%) grade2 (46,7%).

Table 2: Clinical-Pathological Characteristics of 706 "ER (+) / HER2 (-) / Negative Lymph Nodes" BC Cases

Age at diagnosis, mean, median (range), n (%)	Mean = 61, Median = 62, (0-93)
Distribution by age groups, n (%)	
< 40 years	54 (7,6)
40-49	118 (16,7)
50-59	145 (20,5)
60-69	175 (24,8)
70 +	214 (30,3)
Unknown	---
Menopause (yes) n, (%)	538 (76,2)
Personal history of breast cancer, n (%)	66 (9,3)
Family history of breast cancer, n (%)	216 (30,6)
Bilaterality, n (%)	21 (3,0)
Size right breast, mean, median (range); cm, n (%) Size left breast, mean, median (range); cm, n (%)	Mean = 2.30, Median = 2.00 (10.00-01) Mean = 2.18, Median = 1.80 (14.00-0.01)
Histology, n (%) Not infiltrating *Ductal* Infiltrating *Lobular:* *Ductal:* Unknown	 83 (11.8) 24 (3.4) 478 (67.7) 117 (16,6)
Tumor grade (histological grade) n (%) 1 2 3 unknown	 181 (25,6) 330 (46,7) 153 (21,7) 42 (5,9)

3.3 Substitute Parameters Evaluated

The frequency of the presence, in the 706 cases of "ER (+) / HER2 (-) / negative lymph node" BC, of the selected SPs is shown in Table 3. Of the total of 8 parameters, 4 (50%) (Age, ER / PR and Her2 / neu) are present between 96 and 100% of cases. The next most frequently found SP were grade (94%) and size (88.5%). Finally, the least frequent were histology 77.5%) and Ki67 expression (61.5%).

Table 3: Selected Surrogate Parameters Available in 706 "ER (+) / HER2 (-) / Negative Lymph Nodes" BC Cases

Parameters available	n (%)
Age	706 (100)
Histotype	547 (77,5)
Size	625 (88,5)
Grade	664 (94)
Estrogen receptors	706 (100)
Progesterone receptors	703 (99,6)
Her2/neu status	706 (100)
Ki-6 expression	434 (61,5)

3.4 Coincidence Between Substitute Parameters

The percentages in which, in our series, each of the SPs required in the different nomograms is fulfilled and also according to the possibility of a complete application of all SP of each proposed nomogram are shown in table 4. From the total of 10 nomograms selected only in 1 [13] our series can, in the 99.6% of the cases, complete the

required two SPs being them: HR (96, 6%) and the Her2 / neu (100%). In a second nomogram [15] at least 94% of our cases complete the three of the proposed SPs being these: Grade (94 %), ER (100%) and PR (99.6%). In a third nomogram [11] at least 88.5% of the cases complete the required six SPs being these: tumor size (88.5%), patient age (100%), laterality (100%), ER receptor (100%), PR receptor (99.6%) and HER2 / neu (100%). In a fourth nomogram [19] 77,5% of cases complete the required six SPs, being these: size (88,5%), ER (100%), PR status (99,6%), HER2neu (100%), Nottingham (94%) and histomorphology (77,5%). In a fifth nomogram [20] also a 77,5% of the cases complete the required five SPs: age (100%), tumor size (88.5%), grade (94), PR status (99,6) and histologic type (77,5%). Finally, in the five remaining nomograms evaluated [12,14,16-18] the percentage of cases that could complete the required SPs only reached 61.5% of the cases in each of them because this was the percentage of cases in which the Ki67 status study was conducted to evaluate the rate of tumor proliferation.

Table 4: Frequency of Application of Each Nomogram Proposed According to the Available SP in 706 "ER (+) / HER2 (-) / Negative Lymph Nodes" BC Cases

Reference	Published series clinical and pathologic markers required as SP	Frequency (%) of clinical and pathologic markers required as SP available in the series under study	Cases of 706 BC according to possible complete application of the proposed nomogram; n (%)
Auerbach J et al., 2010 [11]	Tumor size, patient age, laterality, ER receptor,PR receptor results and HER2/ neu result	Tumor size (88,5), patient age (100), laterality (100), ER receptor (100) ,PR receptor (99,6) results and HER2/neu (100) result	625 (88,5)
Dellapasqua S et al. 2012 [12]	Age, Histotype, Tumor size, Grade, ER/PgR , Her2/neu status and Ki-67.	Age (100), Histotype (77,5), Tumor size (88,5), Grade (94), ER (100)/PgR (99,6) , Her2/neu (100) status and Ki-67 (61,5)	434 (61,5)
Rouanet R et al., 2013 [13]	HR and HER2 status. HER2-HR+; HER2-HR-; HER2+HR+; HER2+HR-	HR (100/99,6) and HER2 status (100)	703 (99,6)
Turner B et al; 2015 [14]	ER, PR, HER-2, and Ki-67, Nottingham score (NS) and tumor size	ER (100), PR (99,6), HER-2 (100), and Ki-67 (61,5), Nottingham score (NS) (94) and tumor size (88,5)	434 (61,5)
Gage MM et al. 2015 [15]	-Low grade and positive progesterone receptor tumors (LG+PR). -High grade or low estrogen receptor (ER) (ER < 20%) tumors (HG/ LER).	Grade (94), ER (100) and PR (99,6)	664 (94)
Özmen V et al., 2016 [16]	Age, LN Status, Grade, ER score ≤10%, PR score ≤20% and Ki67 score	Age (100), LN Status (100), Grade (94), ER (100) score ≤10%, PR score (99,6) ≤20% and Ki67 (61,5) score	434 (61,5)
Harowicz MR et al., 2017 [17]	Estrogen receptor status and progesterone receptor status along with different combinations of grade, proliferation indices (Ki-67, mitotic rate), HER2 status, and tumor size.	Estrogen receptor status (100) and progesterone receptor status (99,6) along with different combinations of grade (94), proliferation indices (Ki-67 (61,5), mitotic rate), HER2 status (100), and tumor size (88,5).	434 (61,5)

Farrugia DJ et al, 2017 [18]	Magee Equation 3 test: ER, PR, HER2 status and Ki-67.	ER (100), PR (99,6), HER2 (100) status and Ki-67 (61,5).	434 (61,5)
Hanna MG et al., 2017 [19]	Size, ER, PR status, HER2neu, Nottingham and histomorphology.	Size (88,5), ER (100), PR (99,6) status, HER2neu (100), Nottingham (94) and histomorphology (77,5)	547 (77,5)
Orucevic et al, 2019 [20]	Age, tumour size, grade, PR status and histologic type	Age (100),tumour size (88,5), Grade (94), PR status (99,6), and histologic type (77,5)	547 (77,5)

IV. DISCUSSION

BC in Argentina, as we reported earlier, has an epidemiological pattern and an incidence rate typical of a "western" and "developed" country [10] without major variations of both qualifiers in the BC over the last 40 years [21] We also report that, with the resources currently available, the BC can be staged properly, according to the latest version of the TNM, in 75% of cases [22]

That a subset of no more than 706 (38.5%) of "early" BC *"ER (+) / HER2 (-) / negative nodes"* come from a database of 1832 new cases of BC, (stages I-IV) recorded between 2012 and 2014, presents its logic. The highest incidence of the whole "early stages" BC in developed countries, due to a massive and continuous use of mammogram screening in these populations [23-25] entails a high frequency of *"ER (+) / HER2 (-) / negative nodes"* BC. On the contrary, in our population, although the mammography is known and applied, but not in a massive and systematic way the frequency of this kind of BC *("ER (+) / HER2 (-) / negative nodes")* is related to a lowest diagnosis of the whole types of "early stages BC" [10,22].

Genomic platform tests are now considered "standard of care" to maintain treatment decision-making for patients *"ER (+) / HER2 (-) / negative lymph node"* BC. Previous analyses of genomic platforms testing have assessed hypothetical cohorts under ideal conditions and concluded that testing had low costs relative to its benefits; the application of gene panels in clinical practice avoids overtreatment, with its possible adverse effects, in the short term and toxic in the longer term [26-28] as well as reducing treatment cost [29-31]

MIC countries, such as Argentina, where gross national income per capita is between US$9,950 and $12,055 per year [32] are mainly characterized by fragmented and poorly coordinated medical care, moderate or high levels of poverty and disparities to access a basic standard of care not only for cancer but also for other complex diseases beyond of being covered by law. Patients in the public environment cannot pay for targeted therapy, so there are currently no hospital laboratories offering genomic platforms.

OncotypeDx® is expensive [the current estimated cost is U$4000 [9]. The cost of the study is the main reason for the almost no realization in the past (2012-13) and nowadays in the MIC countries such as Argentina. None of the health sub-sectors recognizes this study (not included in the oncological diagnosis and treatment protocols accepted by law in our country) for which they do not reimburse their cost. The few cases performed were done privately, paid by the patients and performed abroad the country. For all the mentioned the current tendency, encouraged by research groups, is to use clinic pathologic variables for prediction of low-risk or high-risk OncotypeDx® Recurrence Score (ODXRS) using nomograms models.

Quality prediction models depends on the amount and quality of data derived. In some aspects of the diagnosis of BC our country performs better than expected due to its economic development level. For example, immunohistochemistry (IHC) for HR and Her2 / neu is performed routinely in a high percentage of cases, in almost most laboratories for at least more than a decade. As such, IHC is an accessible and relatively inexpensive test and one that can be performed quite quickly. This is in sharp contrast to genomic

test that are routinely performed abroad in the country resulting in a prolonged time of realization and increased costs. Having, in our series, the results of HR and Her2 / neu in almost all cases, this allows us to apply 5/10 of the selected nomograms in which these required SPs are available between 88.5% and 99.6% of the cases. On the contrary, when it is necessary to know the proliferation index studied by the Ki67 expression as SP to fulfill a nomogram, this data is only present in 61.5% of the cases in the remaining 5 nomograms.

V. CONCLUSION

Despite the fact that MIC oncologists are theoretically well informed in the use of genomic platforms [8,33-36] they are far away from developed in the real-world a practice based in precision oncology; this kind of practice is a great challenge for them and frequently limited, when it is possible, to private practice.

Our study, despite its limitations, provides some evidence for the design and orientation in our country of health policies and diagnostic interventions such as nomograms in the treatment of BC cancer, especially in early stages. These nomograms are useful tools to help to decide whether further OncotypeDx® testing is necessary and are excellent surrogates for patients for which OncotypeDx® testing is not affordable or even available. We demonstrate that, although there are gaps in the updated care process (for example: genetic profile) of BC, it is possible to use nomograms in our country through a comprehensive and complete collection and a careful subsequent analysis of the conventional parameters present in the diagnosis of BC. Special emphasis should be noted on the histopathological and immunohistochemical results, available almost routinely in our series, a fact that allows us to evaluate the RS and thus apply the corresponding therapy trying to achieve results similar to those that would be obtained with the use of GP.

Addendum: while the present work was being carried out, a pandemic was hitting the world. COVID 19 has a major negative effect on stretched health care systems in low- and middle-income countries and also places a financial burden on households. Our country with 4100 000 of cumulative number of confirmed cases and 85075 cumulative number of confirmed deaths (between March 20, 2020 and June 12, 2021) is now obliged to invest abundant health resources in the fight against covid. The new needs would make it very difficult to develop, in the immediate future, new and expensive methodologies such as, for example, genetic study,

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards, the National Law 25326 of Habeas Data Personal Data Protection and the National Patient Rights Act 26529. For retrospective studies (applies to our study): “for this type of study formal consent is not required”.

Conflicts of Interest

The authors declare no conflict of interest.

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A Comparison of Logistic Regression, Modified Logistic Regression and Naïve Bayes Models for Classifying HIV Viral Load Suppression: The Case of Zombo District in Uganda

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ABSTRACT

Purpose: To enhance the performance of the logistic regression by integrating step-wise procedures and henceforth compare and evaluate its performance with the Logistic regression and Naïve Bayes in classifying HIV viral load suppression (VLS).

Methods: Models for classifying VLS were built using Logistic regression, modified logistic regression and Naïve Bayes classifiers. Accuracy, balanced accuracy and the area under the receiver operating characteristics curve (AUC) were the key performance metrics used to evaluate the generalizability of the various classifiers.

Results: The modified logistic regression model trained on fewer predictor attributes achieved an accuracy of 84.9%, a balanced accuracy of 83.8% and an AUC of 92.6%. The traditional logistic regression model trained on a full set of predictor attributes achieved an accuracy of 84.9%, a balanced accuracy of 83.6% and an AUC of 92.5% whereas the naïve Bayes model achieved an accuracy of 81.6%, a balanced accuracy of 80.5% and AUC of 89.4%.

Keywords: comparison, logistic, modified, naïve bayes, classification, viral load suppression.

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Conclusion: The modified logistic regression model outperformed the traditional logistic regression and naïve Bayes models on account of recording higher balanced accuracy and AUC values of 83.8% and 92.6% respectively albeit with fewer predictor attributes. Hence integrating step-wise regression procedures in the traditional logistic regression model can enhance its classification performance leading to better predictions.

Keywords: comparison, logistic, modified, naïve bayes, classification, viral load suppression.

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I. INTRODUCTION

Logistic regression and Naïve Bayes are among the most used data mining classification techniques [1]. This might be because they have algorithms that are easy to implement [2, 3], their ability to handle both continuous and discrete data [1], application of probability theory in their classification modelling [4] and they produce real-time predictions that can be easily interpreted [5].

The Logistic regression classifier assumes the absence of multicollinearity among the predictors while conducting classifications [6]. However, the performance of the Logistic regression classifier is usually weakened by the presence of multicollinearity among the predictors which may lead to poor classifications [7]. A study by Senaviratna & Cooray [8] reported that the best solution is to understand the cause of multicollinearity and remove the highly correlated variables in the model. However, O'Brien [9], objected to removing the correlated variables from the model because less information would be available potentially leading to suboptimal model performance. Despite this weakness associated with the Logistic regression classifier, several scholars [10, 11, 12] have independently employed the logistic regression classifier while undertaking classification tasks.

Scholars [13, 14] have recommended the use of the Bayesian approach premised on Bayes' theorem as an alternative to the Logistic regression classifier to overcome the problem of multicollinearity because its assumption of mutual independence among the predictors enables each distribution to be independently estimated. Several scholars [15, 16, 17] further stressed that the Naïve Bayes classifier has superior strengths such as being efficient, computationally fast, and does not require a lot of data for training to conduct classifications. Owing to its strength, the Naïve Bayes classifier has outperformed the Logistic Regression classifier in various fields [3, 18, 19] to provide accurate and reliable results. Asharaf et al., [20] recommended the need for more comparative studies of the different data mining techniques to determine their classification ability so that the most optimal model can be chosen. Above all, a number of approaches have been proposed to improve the goodness of fit of the traditional logistic regression classifier in order to overcome its multicollinearity bottlenecks [21, 22]. These include Principal Components Analysis (PCA) [23], Monte Carlo simulation [24] and Variance Inflation factor (VIF) [25], which drops predictors with high VIFs.

Motivated by the performance improvement of enhanced independent classifiers [26] coupled with the fact that stepwise regression procedures are more likely to have lower false classification rates [27]. This study proposes a modified logistic regression classifier which employs the VIF integrated with step-wise regression due to its simplicity [21].

1.1 HIV Viral Load Suppression as a Case Study

HIV viral load suppression (VLS) is the ultimate measure of treatment success for People Living with HIV/AIDS (PLHIV) receiving antiretroviral therapy (ART) [28]. This is in line with the third Sustainable Development Goal (SDG 3) premised on the commitment made by the United Nations (UN) member states to end the AIDS epidemic by 2030 by achieving 95% VLS by 2025 [29, 30]. The consolidated guidelines on the use of ART drugs for treating and preventing HIV infection define all PLHIV receiving ART with HIV viral load (VL) less than 1000 copies/mL as having a suppressed VL [28]. According to the Annual Health Sector Report for the Financial Year 2021/2022, Zombo District achieved VLS of 71% [28]. This falls below the national VLS rate for Uganda of 82% [29] and also below the UNAIDS 95-95-95 target of at least 95% VLS by 2025. Despite several efforts to improve the treatment outcome of PLHIV receiving ART outcome through health education, infrastructural development, bridging the human resource gaps and strengthening the supply chains for essential commodities [31], so little is known about the key factors associated with VLS as well as the performance of various classifiers in determining these factors among PLHIV on ART in Zombo District.

1.2 Classifier Evaluation Metrics

Evaluating the performance of a classifier is paramount as it permits researchers to compare competing models as well as determine the degree to which its results can be generalized to an unseen sample or population from the same distribution from which the existing data were drawn [32]. Several scholars [33, 34, 35] attest that the confusion matrix; which provides a summary of classification outcomes, is the commonest way for evaluating classifier performances.

On the other hand, presenting a confusion matrix by itself in the absence of a suitable summary statistic or metric is insufficient and easily leads to biased interpretations of performance [32]. The most utilized summary statistic emanating from the confusion matrices is accuracy, defined as the number of correct predictions across all classes [36, 37]. However, classification accuracy is a misleading performance metric particularly when the data are not perfectly balanced [36, 38].

The balanced accuracy metric, defined as the arithmetic mean from both the minority and majority classes was suggested to address the above limitation [32]; thus providing more reliable performance evaluations for imbalanced data [39, 40].

1.3 Problem Statement

Many scholars have independently employed logistic regression for classification problems. However, the performance of the Logistic regression classifier is usually weakened by multicollinearity among the predictors which may lead to poor classification results. Naïve Bayes has been suggested as an alternative classifier to overcoming multicollinearity as it assumes mutual independence among the predictors. To this end, limited research has been done to enhance the performance of the logistic regression as well as compare its performance with respect to the naive Bayes classifier.

In order to deal with the existing multicollinearity challenges of the traditional logistic regression classifier, this paper proposes a modified logistic regression classifier which employs a step-wise procedure based on VIFs and hence compare and evaluate its performance with the traditional logistic regression and naïve Bayes classifiers on a similar dataset to determine the most optimal classifier.

II. METHODS

2.1 Data Preprocessing

2.1.1 Data Sources

Data was extracted from Patient forms in one Hospital and nine health facilities of level three (HC IIIs) in Zombo District [41] that are accredited to offer antiretroviral therapy (ART) services for PLHIV who were newly initiated on ART between February 2020 to May 2022. This period conforms with the revised ART guidelines that specify the evaluation of VL for all newly identified PLHIV started on ART after six months of ART treatment [42, 43]. The extracted variables and their descriptions are indicated in Table 1.

Table 1: Description of Variables used in this Study

Sn	Variable Name	Description	Variable Type	Categories
1	HIV Clinic No.	Unique Number is assigned to the HIV patient upon being enrolled on care at the ART clinic in a health facility		
2	Age	Age of the HIV patient in completed years	Continuous	This was transformed into four (4) categories namely; 0 – 9 years, 10 – 19 years, 20 – 49 years, 50 years and above
3	Gender	Gender of the HIV patient	Categorical	M-Male, F-Female
4	Marital	Marital Status of the HIV patient	Categorical	Married, Never Married, Separated, Widow
5	Stage	HIV WHO Clinical Stage of the patient	Categorical	Stage 1, Stage 2, Stage 3, Stage 4
6	regimen	ART regimen	Categorical	DTG-based regimen, LPV-based regimen, NPV-based regimen
7	freq	Daily ART dosage drugs	Categorical	Once per day, Twice per day
8	month_2	HIV patient monthly clinical encounter at the second month	Categorical	Active, Missed Appointment
9	month_3	HIV patient monthly clinical encounter at the third month	Categorical	Active, Missed Appointment, Lost to Follow up
10	month_4	HIV patient monthly clinical encounter at fourth month	Categorical	Active, Missed Appointment, Lost to Follow up
11	month_5	HIV patient monthly clinical encounter at the fifth month	Categorical	Active, Missed Appointment, Lost to Follow up
12	month_6	HIV patient monthly clinical encounter at the sixth month	Categorical	Active, Missed Appointment, Lost to Follow up

Sn	Variable Name	Description	Variable Type	Categories
13	adherence	Adherence to taking ART drugs by the HIV patient during the sixth months period on care	Categorical	Fair, Good, Poor
14	Disclosure	Disclosure of HIV status by the client	Categorical	Yes, No
15	VLS	HIV Viral Load Suppression outcome after 6 months of being on HIV care.	Categorical /Binary variable	0=Suppressed, 1=Non-Suppressed

A total of 1,757 records were extracted, each denoting a newly identified PLHIV started on ART after six months of ART treatment.

2.1.2 Data Cleaning

The researchers examined the data set for missing values, outliers, and addressed discrepancies and observations with missing values were excluded [44].

2.1.3 Data Transformation

Given that the dataset contained both continuous and categorical variables, data discretization was used to create homogenous groups of continuous predictor variables, reducing outliers and minimizing noise formation [45].

2.1.4 Training and Validation Datasets

The researchers split the dataset into training and testing datasets. 70% of the dataset was assigned to the training group for the development of the classifiers. The rest of the dataset (30% of the total cases) was assigned to the validation groups for the assessment of model performance [46].

Analysis

The following classifiers were employed;

Naïve Bayes: It utilizes the Bayes theorem [47] to compute the posterior probability of dependent variable Z given predictor variables $Y = (y_1, y_2, \ldots, y_n)$ the following equation (1).

$$P\left(\frac{Z_n}{y_1, y_2, \ldots, y_n}\right) = \frac{P(Z_n)\prod_{i=1}^{n} P\left(P\left(\frac{y_i}{Z_n}\right)\right)}{\prod_{i=1}^{n} P(y_i)} \quad (1)$$

Where $P(Z_n)$= the probability of Z to be observed

$P(y_i)$= the probability of y to be observed

$P\left(\frac{Z_n}{y_i}\right)$= the posterior probability of class (Z) given predictor (y).

$P\left(\frac{y_i}{Z_n}\right)$= the probability of observing y given Z holds

Since the naïve Bayes assumption is that predictors $(y_1, y_2, \ldots, y_n)$ are conditionally independent of the response variable Z , the posterior probabilities $P\left(\frac{Z=1}{Y}\right)$ and $P\left(\frac{Z=0}{Y}\right)$ are computed for a new sample by dropping the denominator in equation (1) as illustrated in equation (2).

$$x = argmax(P\left(\frac{Z_n}{y_i}\right) = P(Z_n)\prod_{i=1}^{n} \quad (2)$$

Where x is the class of the response variable with the highest probability given a set of variables.

Logistic regression: It uses numerical and or categorical predictors to estimate the likelihood of a dichotomous response variable [5]. The logistic regression model can be expressed as;

$$\log log\left(\frac{P(y_i=1)}{P(y_i=0)}\right) = \alpha + \beta_1 x_1 + \quad (3)$$

Where Y denotes the response variable

x_i denotes the predictor variables

β_i denotes the coefficients of the predictor variables

α denotes the intercept

The probability of p_i is represented by equation (4)

$$p_i = \frac{1}{(1+e^{-x\beta})} \quad \in[0,1] \quad (4)$$

2.1.5 Proposed Modified Logistic Regression

The researchers integrated the backward stepwise regression process [48] into the traditional logistic regression indicated in equation (iii) in order to determine the importance of each predictor variable [49].

The researchers commenced with a full classifier and kept removing predictor attributes with the least significant values (highest P-values>0.05; variables that worsen the model highest), to the trained model, one at a time. For every removal, the trained modified logistic classifier was fit/generalized onto test data until the stopping criteria were met. The criteria to terminate was achieving balanced accuracy metrics similar to or higher than those returned by the traditional logistic regression classifier. The above process was repeated until only variables that generated a parsimonious model were retained in the classifier

2.1.6 Goodness of fit

The 10-fold cross-validation method was employed to validate the accuracy, sensitivity, specificity and balanced accuracy of the classifiers [33] as indicated the equations (5) (6), (7) and (8);

$$Accuracy = \left(\frac{TP+TN}{TP+TN+FP+FN}\right) \quad (5)$$

$$Sensitivity = \left(\frac{TP}{TP+FN}\right) \quad (6)$$

$$Specifity = \left(\frac{TP+TN}{TP+TN+FP+FN}\right) \quad (7)$$

$$Balanced\ Accuracy = \left(\frac{Sensitivity+Specificity}{2}\right) \quad (8)$$

Where in the context of this study, the entries in the confusion matrix were defined as.

1. True positive (TP): is the number of actual "NO" VLS cases classified as "NO".
2. False-positive (FP): is the number of actual "YES" VLS cases classified as "NO"
3. False Negative (FN): is the number of actual "NO" VLS cases classified as "YES".
4. True Negative (TN): is the number of actual "YES" VLS cases classified as "YES".

Software

The data processing and analysis were carried out in R, version 4.1.2 [50], using the R packages "dplyr" version 1.0.7 [51], "caret" version 6.0-90 [52], "pROC" version 1.18.0 [53] and "ROCR" version 1.0-11 [54].

III. RESULTS

In this section, the researchers first present the results from each classifier and then present the comparison results.

3.1 Key Variables for Classification of VLS

Results revealed that fourteen (14) out of 25 variables were key for classifying VLS, namely; "never married", "HIV WHO clinical stage 3",

"HIV WHO clinical stage 4", "daily ART dosage twice", "month 3 lost to follow up", " month 4 lost to follow up", "month 4 missed appointment", "month 5 lost to follow up", "month 5 missed appointment", "month 6 lost to follow up", "month 6 missed appointment", "good ART drug adherence", "poor ART drug adherence" and "disclosure of HIV status by the patient".

Table 2: Key Variables for Classification of VLS for the Logistic vs Modified Logistic Regression Models

Model	Accuracy(%)
Traditional Logistic regression model with all variables (25)	84.9
Modified Logistic regression model with fewer variables (14)	84.9

Table 2 reveals that when the modified logistic regression is trained on the dataset, the number of predictor variables is reduced from 25 to 14. This implies that the modified logistic regression model was able to achieve the accuracy of the traditional logistic regression trained on a full set of variables at the expense of some irrelevant or correlated variables. Hence the resultant variable subset using the modified logistic regression is the most significant set of variables that improves the predictive accuracy of VLS and thus a more robust model for determining VLS.

3.2 Comparison of the Classifiers Performance

The performance of the classifiers was evaluated based on their capacity to classify the instances of the data set into "YES" and "NO" VLS. The researchers utilized 10-fold cross-validation to assess the performance of the three classifiers on previously unlearned data. Computation of the performance metrics indicated in equations 8-11 revealed the results indicated in Fig. 1.

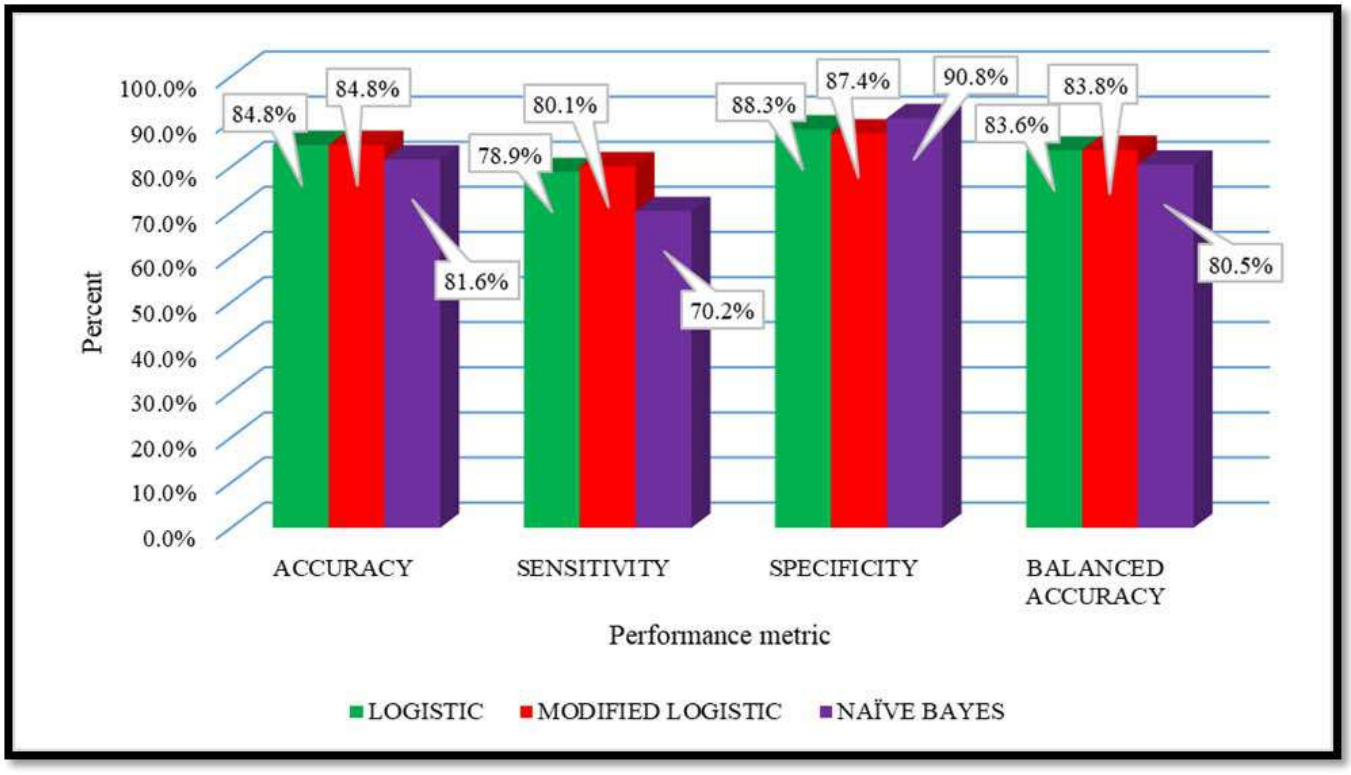

Fig. 1: Comparison of Classifiers' Performance Using 10 Fold Cross-Validation

According to *Fig. 1,* the modified logistic regression model attained the highest performance with respect to the accuracy, sensitivity, and balance accuracy metrics recorded at 84.8%, 80.1%, and 83.8% respectively. This implies that this model correctly classified 84.8%

(accuracy) of PLHIV whose viral load was either suppressed or not suppressed. Additionally, this model also correctly classified 80.1% of PLHIV whose viral load was not-suppressed.

On the other hand, the naïve Bayes classifier registered the highest specificity at 90.8% compared to 88.3% registered by traditional logistic regression and 87.4% obtained by the modified logistic regression classifier. The achieved balanced accuracy results indicate that the proposed modified logistic regression model outperformed the traditional logistic regression and naïve Bayes classifiers by 0.2% and 10.3% respectively.

Comparatively, raw data in Table 1 revealed that the response variable (VLS) comprised uneven proportions of 36% suppressed VL and 64% suppressed VL and therefore the balanced accuracy metric was used as the overall evaluation which balances the precision and recall metrics across each response variable class [55].

3.2.1 Receiver Operating Characteristics (ROC) Curve

The ROC curve *(Fig. 2)* is a graphical illustration of the relationship between the performance of a classifier's sensitivity and specificity [42]. The ROC enabled the researcher to evaluate how well the developed models performed at different thresholds. *Fig. 2* shows that the Modified logistic regression, traditional logistic regression and naive Bayes classifiers' corresponding Area under the Curve (AUC) values were 92.6%, 92.5% and 89.4%. A random model would simply divide the graph in half, giving it an AUC of 50%. For this reason, the classifiers' produced ROC curves supersede a random model, showing that the applied models provide a good measure of separability.

The purple line, which denotes the modified logistic regression, generated a superior cut-off decision level than the other two classifiers since it maximised the true positive rate at the lowest level of false positives (1-specificity).

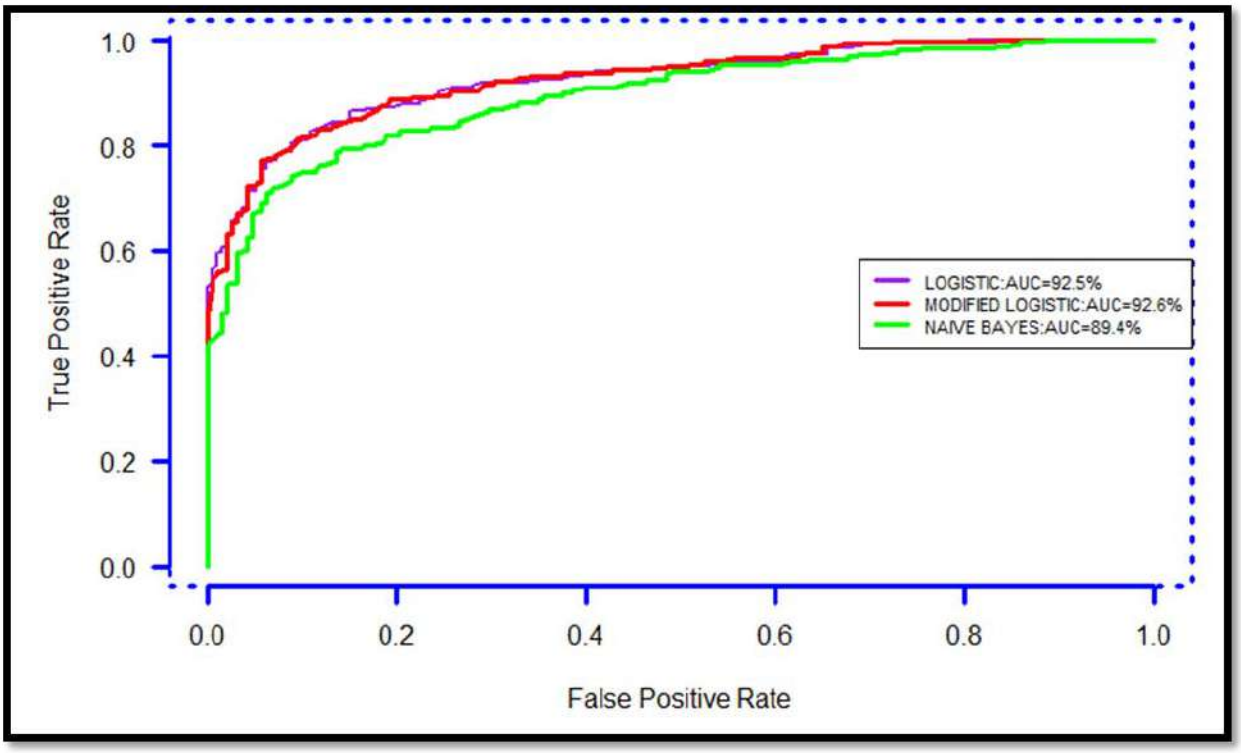

Fig. 2: Comparison of the ROCs for the Classifiers at Various Thresholds

IV. DISCUSSION

The purpose of this study was two fold. Firstly, to enhance the performance of the traditional logistic regression classifier and secondly, to compare and evaluate the performance of the traditional logistic regression, modified logistic regression and Naive Bayes models in classifying VLS. The findings showed that the modified

logistic regression classifier slightly outperformed the traditional logistic regression and naïve Bayes classifiers with regards to accuracy, sensitivity and balanced accuracy whereas the naïve Bayes performed best in terms of specificity.

The proposed modified logistic regression classifier inherits properties of the backward stepwise regression algorithm. This implies that integrating the step wise regression procedures into traditional data mining classifiers can enhance their classification performance as evidenced by the better performance of the modified logistic regression classifier when fitted on previously unknown data samples. This phenomenon is in agreement with those of previous studies [56, 57, 58] that reveal that the performance of the traditional data mining classifiers can be improved by integrating it with other machine learning techniques. In terms of key determinants of VLS, our findings were consistent with those of [59, 60, 61, 62].

Conversely, the study faced a key challenge of available data being limited to data whose variables were regularly gathered from patients and caretakers and recorded in the patient medical records systems for the period under investigation hence the researchers were unable to subject the developed modified model to a higher dimensional dataset in terms of variables and observations from a known population which would return more reliable and robust performance results [63].

V. CONCLUSION

In this study, a modified logistic regression classifier is proposed to further enhance the classification performance of the traditional logistic regression classifier. Furthermore, performance comparisons were made between the modified logistic regression, traditional logistic regression and naïve Bayes classifiers. We found that the modified logistic regression performed slightly better than the traditional logistic regression and naïve Bayes classifiers on account of recording higher balanced accuracy and AUC values of 83.8% and 92.6% respectively albeit with fewer predictor attributes. We attribute this to the fact that the modified logistic regression adapts a step-wise regression procedure which uses a linear combination of the best variables to form a robust classifier, unlike the traditional logistic regression and naïve Bayes. Hence integrating step-wise regression procedures in the traditional logistic regression model can enhance its classification performance leading to better predictions.

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Conflicts of interest/Competing interests: The authors declare that they have no conflict of interest

Availability of data and material: The data was sourced from the Patient forms in one Hospital and nine health facilities of level three (HC IIIs) in Zombo District, Uganda and it has been availed/ uploaded as supplementary material.

Code availability: The program scripts/code can be availed by the corresponding author upon request

Authors' contributions: JS was involved in drafting the proposal, data collection, data preprocessing, data analysis, model designing and writing the manuscript. FFB was also involved in data analysis, model designing and writing the manuscript. DC and FB were supervisors of the work. All authors read and approved the final manuscript.

Ethical considerations: The data were accessed with official permission from Zombo District Health Office and personal identification data was de-identified and treated with the utmost confidentiality.

Research involving human participants: Not applicable. No experiment was performed on animal or human subjects.

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Factors Influencing the Implementation of Maternal and Perinatal Death Surveillance and Response (MPDSR) in Bangladesh: A Scoping Review

MA Halim, ASM Sayem, Minjoon Kim, Md Ziaul Matin, Abu Sayeed Md. Abdullah, Sifat Parveen Sheikh, Moonmoon Islam Khan, Azizul Alim & Fazlur Rahman

ABSTRACT

The Maternal and Perinatal Death Surveillance and Response (MPDSR) is a system to identify, report and create mechanisms for reducing preventable maternal and neonatal deaths, and stillbirth. MPDSR has been implemented in Bangladesh in the last decade. This study was conducted to identify the factors including the barriers and enablers influencing the implementation of MPDSR within the existing health system in Bangladesh.

We conducted a scoping review for literature published between 1999 to 2019. Two reviewers selected the articles based on a scoping review technique usingthe Prisma flow checklist and diagram. The articles were collected from search enginessuch as PubMed and Google scholar, and also from websites of public andprivate organizations, and United Nations (UN) Agencies. We synthesized the available evidence on barriers and facilitators of the current MPDSR process in Bangladesh.

Keywords: MPDSR, maternal deaths, neonatal deaths, barriers, enablers, scoping review, Bangladesh.

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Factors Influencing the Implementation of Maternal and Perinatal Death Surveillance and Response (MPDSR) in Bangladesh: A Scoping Review

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ABSTRACT

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The search process identified 890 journal articles, 100 different guidelines and reports; 11 of them met the inclusion criteria for enablers and barriers of MPDSR implementation in Bangladesh. The enablers included interdisciplinary teamwork with good communication, capacity development, evidence from MPDSR review meetings leading to improvements in health services, coordination, and organized supervision and monitoring. The barriers included difficultiesincollecting data from hard-to-reach areas, ensuring the quality of data, limitationsinrecord keeping, social barriers, lack of effective coordination and planning for a timely response, limited human resources capacity, lack ofmotivation among the staff, varying levels of training and competence to identify complications, lack of supervision and poor implementation of guideline.

The findings from this scoping review can guide policy makers in addressing and overcoming the barriers of MPDSR implementation in Bangladesh.

Keywords: MPDSR, maternal deaths, neonatal deaths, barriers, enablers, scoping review, Bangladesh.

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I. INTRODUCTION

Bangladesh has been implementing MPDSR program through government health system to notify and subsequently investigate the causes of maternal and perinatal deaths occur both in the communityand in the health facilities (1). Verbal autopsies and facility death reviews are conducted for those deaths identified for causal analysis. The data from MPDSR are entered into government District Health Information System-2 (DHIS-2).

MPDSR data, available through DHIS-2, offers the opportunity to calculate rates/ratio of maternal and neonatal death while verbal autopsies allows the understanding of socio-demographic factors, care-seeking pattern and causes of deaths (2).

The MPDSR program in Bangladesh was first piloted in 2010 and then expanded to ten districts in 2015 (3). The program was later updated by adapting country experience and the MPDSR guidelines of World Health Organization (WHO) (4). The government of Bangladesh then incorporated it in the national health sector program. UNICEF Bangladesh with other partners is providing technical assistance to the government for implementation of MPDSR countrywide (5).

The MPDSR cycle starts with notification of maternal and neonatal deaths including stillbirths at the community and health facility by the community-level health and family planning workers and nurses in the health facilities (6). For identifying causes of deaths, verbal autopsies at the household level and facility death reviews at facilities are conducted. Social autopsies are conducted in the community to look into the social causes of deaths. The causes of deaths are assigned and validated in regional workshops by obstetricians, pediatricians and program experts using data from verbal and social autopsies. On the other hand, the maternal and neonatal deaths, and stillbirths that occur at district and upazila (administrative sub-unit of district in Bangladesh) level facilities are notified by nurses/Family Welfare Visitors (FWVs) and the death review and cause analysis is done by the doctors, obstetricians, pediatricians and managers using facility based death review guideline and tools (7).

The MPDSR data is entered into the DHIS-2 that allows real-time access and utilization of data (6) by MPDSR committees at district and upazila level to formulate responses: action plans for implementation- a data-driven decision-making process at both national and subnational levels (8). The program has enabled decision-making in terms of allocation of resources, capacity-building of health workers for improvement of existing service delivery and quality of care and introducing new services for reducing preventable maternal and perinatal deaths (7).

Evidence from low- and middle-income countries (LMICs) shows that availability of healthcare data can support decision-making (9). MPDSR implementation in LMICs aims to ensure that all maternal, neonatal deaths and stillbirthsare reported and compel healthcare administrators to take actions to reducematernal and neonatal deaths effectively (9). In Sub-Saharan Africa (SSA), the reduction of maternal and neonatal deaths has been found to be strongly correlated with the presence of a national Health Management Information System (HMIS) (10,11).

As an LMIC, Bangladesh has made remarkable progress in implementing MPDSR while experiencing certain challenges and facilitators. Understanding these enablers and barriers in MPDSR implementation can help in improving the process and overcoming the gaps in implementation.In this scoping review, we explored the factors including the barriers and enablers influencing the MPDSR implementation in Bangladesh.

II. METHODOLOGY

A scoping review was conducted to meet the objective of the study (11). The scoping review addressed the following research question: *What factors influence the implementation of MPDSR in Bangladesh?*

We prepared a comprehensive list of articles and documents of potentially relevant topics using electronic search. Those included original peer-reviewed journal articles, grey literature, relevant guidelines, policy papers, conference proceedings, unpublished studies, and program reports. We used keywords for the electronic search [Table 1]and kept records of documents with the dates of inclusion for each database searched. A reference management tool was used for bibliography, citation and elimination of duplicate records. The databases were last searched on February 28, 2022.

Table 1: Sources of Documents (Grey literatures and the journal articles)

Search Engines	Grey Materials	Keywords
• Google Scholar • PubMed • Google	• DHIS-2 • Government websites: Directorate General of Health Services (DGHS), Directorate General of Family Planning (DGFP), Ministry of Health and Family Welfare (MoH&FW) • Website of relevant non-government organizations (NGOs), International NGOs (INGOs) and UN Agencies: WHO, UNICEF, UNFPA, Save the Children etc.	• Maternal Death Surveillance System, • Maternal and neonatal death review system, • Bangladesh, • MPDR, • MPDSR, • Barriers of MPDSR implementation, • Enablers of MPDSR implementation,

After eliminating duplicates, we screened titles and abstracts based on inclusion criteria set for the selection process. Selected full text articles were obtained for second stage screening. The inclusion criteria of this scoping review are as follows:

- Documents relevant to MPDSR.
- Settings: Bangladesh.
- Published between 1999 and 2019.
- Published both in English and Bangla languages.
- Guidelines, policy briefs, evaluation reports, training manuals, pocketbooks, abstracts, grey literatures and peer-reviewed journal articles.
- Study conducted in Bangladesh (to identify MPDSR implementation programs, enablers, barriers, recommendations).

The following four steps were followed using a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow (Figure 1).

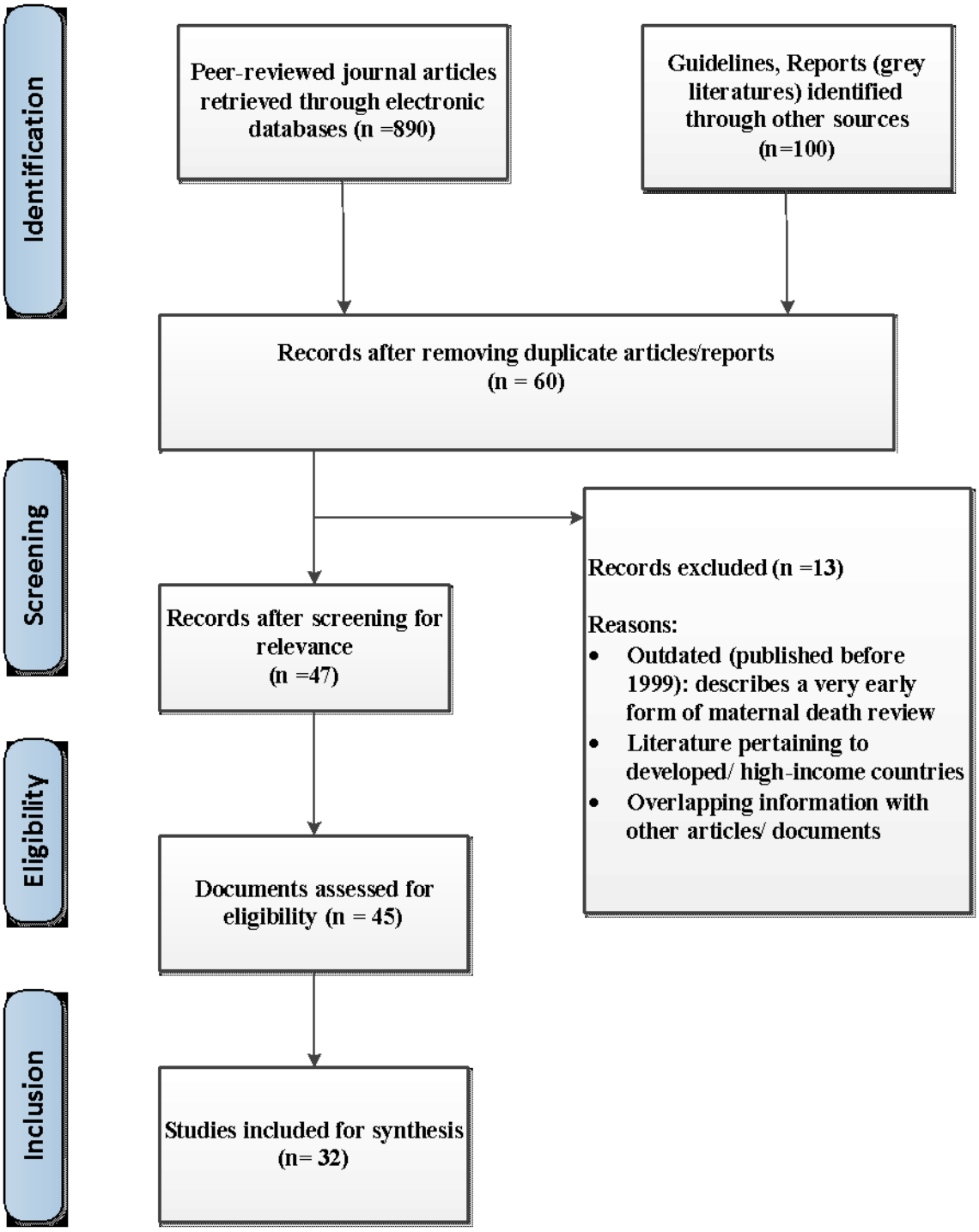

Figure 1: PRISMA Flow Diagram for Review of Articles and Reports

Steps of selecting documents for scoping review

Step 1

Based on the inclusion criteria, the scoping review was conducted to understand enablers and barriers of MPDSR in Bangladesh.

Our exclusion criteria included documents published before 1998, studies conducted in high income countries (HICs), published in languages other than English and Bangla and documents with overlapping findings.

Step 2

Through Google Scholar, PubMed and Google, we searched for documents using keywords: ["Maternal and Perinatal Death Surveillance and Review (MPDSR)" OR "Maternal, Perinatal Death Review (MPDR)" OR "Maternal and neonatal

death review system" OR "Facility Death Review" OR "Maternal Death Surveillance System" OR "Verbal Autopsies" OR "Social Autopsies] AND ["Implementation factors" OR "enablers, barriers" OR "facilitators, challenges"] AND ["Bangladesh"]

Step 3

The search initially identified 990 documents. Screening of the documents were done for duplication and 930 articles and documents were omitted. Additional screening was done to verify whether the remaining documents meet the inclusion criteria or not. Finally, 32 documents were found eligible for review during the study.

Step 4

All documents selected were read thoroughly to understand the enablers and barriers of MPDSR implementation. The review looked into the enablers and barriers of implementation of MPDSR. The findings in terms of search engine, the type of the documents, year of publications and place of study or program, the enablers or facilitators were recorded in an excel sheet.

A study quality checklist was developed to determine the relevancy of conducted studies to MPDSR in Bangladesh and other countries with similar context along with enablers and barriers and recommendation for implementing MPDSR. The results were analysed and presented in the form of tables using MS Excel.Based on the analysis of results, relevant findings like barriers, enablers of MPDSR implementation were gathered.

Ethics approval: This project was approved by the Ethical Review Committee of CIPRB (approval number CIPRB/ERC/2020/08). Though this paper is a review of existing literature and includes no primary data collection from study subjects, we obtained ethical approval as this study was part of a larger implementation research.

III. RESULTS

3.1 Selection of Records

The initial search revealed 890 articles and 100 guidelines. The articles were screened by two reviewers. After removing the duplicates, 60 distinct potential articles/ reports were identified. Then 47 were identified after screening for relevance and then screened through assessing eligibility. Articles pertaining to other LMICs were excluded (n=32). Finally, 15 articles/ reports that were relevant to Bangladesh only were included through proper synthesis for this study [Figure 1; Table 2]. The selected studies were published between 1999 and 2019 [Table 2]. The findings were synthesized for exploring the enablers and barriers in implementation of MPDSR in Bangladesh.

Table 2: Summary of Key Studies with MPDSR Enabler and Barrier Domains

Author	Type	Year	Country	Study design	Enabler domain					Barrier domain				
					Community engagement	Availability of guideline, Action Plan	Monitoring & supervision	Engage-ment of focal person	MPDSR data in DHIS-2	Delay in death notification	Poor causal analysis	Lack of local level action	Lack of HR/logistics	Lack of coordination
Adams A et al (9)	Journal Article	2015	Bangladesh	Realist Evaluation	√		√	√			√			
Ministry of Health and Family Welfare (1)	Guide line	2016	Bangladesh	Participatory approach to create standardized guidelines and tools	√	√	√							
Biswas A el al (15)	Journal Article	2016	Bangladesh	Qualitative assessment of documents, observations, focus group discussions, group discussions and in-depth interviews by content and thematic analyses.						√		√		√
World Health Organization (17)	Regional Meeting Report	2016	South-East Asia Region	Review of relevant documents, Proceeds from regional meeting		√			√					√
Halim A et al (7)	Journal Article	2014	Bangladesh	Mixed method study on cause and factors of maternal mortality in Bangladesh	√		√					√		
Biswas A et al (5)	Journal Article	2015	Bangladesh	Qualitative study with healthcare providers involved in Facility Death Review: FGDs, IDIs, document review			√	√			√			
Biswas A(22)	Book: Doctoral Dissertation	2015	Bangladesh	Both quantitative and qualitative methods	√	√	√		√					
Biswas A et al (4)	Journal Article	2017	Bangladesh	Progress of MPDR system in Bangladesh, review of existing evidence of maternal and perinatal death review in Bangladesh	√					√		√		√
Khanam RA et al (21)	Journal Article	2009	Bangladesh	Descriptive Study with cross-sectional design			√	√		√				√

Halim, Biswas A,(24)	Program Report	2016	Bangladesh	Progress report on MPDSR implementation and scale-up in Bangladesh	√		√	√		√	√			
Ministry of Health and Family Welfare (30)	Pocketbook	2017	Bangladesh	Instructions to the frontline healthcare provider for MPDSR implementation steps	√	√	√	√	√					
Biswas A et al. (31)	Journal Article	2016	Bangladesh	Economic cost evaluation of death review system in Bangladesh	√			√						
Biswas A et al. (3)	Journal Article	2014	Bangladesh	Mixed methods study to identify the effects of Maternal and Neonatal Death Review at the community level in Bangladesh.	√	√	√	√						
National Institute of Population Research and Training (NIPORT), International Centre for Diarrhoeal Disease Research, Bangladesh (icddr, b), and MEASURE Evaluation (32)	Survey Report	2017	Bangladesh	Survey to assess maternal mortality rates in Bangladesh									√	√
Biswas A et al. (6)	Journal Article	2018	Bangladesh	Descriptive review of social autopsy and its role in MPDSR	√			√						√

3.2 Factors Influencing the Implementation of MPDSR

Based on the evidence available on MPDSR in Bangladesh (Table 2), the scoping review identified important factors (enablers and barriers) of implementation. The major enablers and barriers have been summarized under different levels: community, facility, data flow, both facility and community and national in the following sections:

3.3 Enablers of MPDSR in Bangladesh

Community level: The major enablers included the involvement of the community people (10), high level of commitment from the Community Health Workers (CHWs), support from community-based organizations/ local NGOs (10) and good infrastructure development in previously hard-to-reach areas. To involve the people in the community, awareness was built through social autopsy (SA) – a community

meeting discussing on social reasons of maternal and perinatal deaths and ways to prevent them. Moreover, the CHWs acted as important MPDSR has also been implemented in previously hard-to-reach areas like teagardens. A success story involves 35 intervention teagardens of Sylhet Division of Bangladesh. For all maternal deaths in 2019, social autopsies were conducted successfully where 232 participants (105 males and 127 females) attended. Teachers, community leaders, religious leaders, pregnant women and eligible couples participated in these social autopsies. They discussed the social causes of deaths and prepared an action plan to prevent future preventable maternal and neonatal deaths in their community. The local leaders showed their supportin taking steps to reduce maternal and neonatal mortality in the community. The UN agency funding MPDSR in those areas, along with other supporting local NGOs helped in enabling the process with cooperation from the government-assigned focal person in that particular community (7). [Table 3]

Facility level: At the facility level, trained and skilled staff (10) and involvement of interdisciplinary teams (13) supported successful implementation of MPDSR activities. Involvement of nurses, physicians, statisticians helped in accurate reporting of facility deaths among mothers and newborns.

Data flow: MPDSR data has been integrated within the DHIS-2 platform, which helps in informed decision-making and creating action plans by healthcare managers (27) (14). The government has conducted a series of training and motivational programs for capacity building and team work to support all activities starting from death notification followed by entry into DHIS-2; verbal autopsies at household level, social autopsy at community level, facility death review, followed by causal analysis and MPDSR review meetings at upazila and district level for preparing remedial action plan or responses.

Both facility and community: Successful implementation of MPDSR involved a culture of trust and coordination, use and follow-up of Action Plan (1), active engagement of focal person (10) (13) and organized supervision and monitoring(10). One of the key factors that helped in the progress of MPDSR was active engagement of the MPDSR focal person (10), who took the initiative to work in close collaboration with UN agencies and NGOs that provided technical and financial support for local level implementation of MPDSR (13) [Table 3].

National level: Overall, at the national level, the presence of a robust national MPDSR framework and guideline (1), regular monitoring and supervision through video surveillance by QIS(1), regular implementation of national-level TOTs(1) andincorporating MPDSR into national maternal and neonatal health-related policies and Operations Plans (OP) (1), laws-in-progress to ensure death notification (29) and high level of commitment from the government (1). Since the government was highly committed to the SDGs for reducing maternal and neonatal deaths, the MPDSR program was integrated into the Bangladesh national health sector program in 2016 (1). Since then, MPDSR has been widely accepted by national and sub-national level health and family planning policy makers, managers and health care providers as one of the key interventions for reduction of maternal and perinatal mortality. The development partners provided technical support in organizing and developing a system with a robust guideline and framework, those were approved by the government (1). Monitoring and supervision played important role to support and sustain the implementation of MPDSR (1). The Government established a Quality improvement system (QIS) to monitor and assure the quality of MPDSR activities (1). The QIS supported the improvement of MPDSR activities and the outcomes.

3.4 Barriers of MPDSR in Bangladesh

Community level: There were several barriers within the community including underreporting of deaths (15), delay in death notification (DN) (16), delay in conducting VA and inadequacy in identifying the cause of death (4), misinformation (25), lack of cause analysis at the local level (11), no allocation of transportation costs for health workers (17), lack of social action in the community (4) and predominantly male

community health workers in the MPDSR steps (16). Ideally,death notification should occur within three days but in hard-to-reach pocket areas this can take up to a month, which increases the chances of error(18).The shortage of manpower at community level and other priority works of the community health workers led to under-reporting and delayed reporting. Moreover, a majority of male health workers being involved in collecting data on maternal health issues often poses a social and cultural barrier (16).

Facility level: At the facility level, review meetings were not conducted as scheduled (26) and staff assigned to MPDSR were overworked (13). Since MPDSR is integrated within the existing health system, it was challenging for the healthcare providers and other staff assigned in the process, to accommodate additional work in their routine.

Data flow: Barriers related to the flow of data included: server issues/ difficulties in data entry (4), lack of separate database for MPDSR (4), error in data entry (4)(11), inadequate use of ICD-10 coding (28), lack of coordination between the national Civil Registration and Vital Statistics and the MPDSR data (23). Another significant challenge identified in Bangladesh,was ensuring the quality of MPDSR data in the DHIS-2. Though the HMIS in Bangladesh made good progressover the years, there remains some gaps in the data. Health workers could not cover his/her catchment area within the stipulated time for death notification or verbal autopsies. MPDSR data was often collected at the field level by the supporting agencies and then entered into DHIS2 by the government-assigned frontline health workers.

Some discrepancies were reported in the number of maternal deaths notified in the field reports of supporting agencies and that entered into the DHIS2 in the year 2019 (18).Technological difficulties related to the DHIS-2 server, computers and internet connections caused difficulty in data entry at periphery by health workers (4).

The quality of the data was also an issue in the process of individual reporting of events. For example, a data retrvied from DHIS reported 0-28 days as the “Age at death” for a maternal death, erroneously reported from a possibleneonatal death. The death analyses data reflected errors. In some cases, causes of maternal deaths were attibuted to road traffic accident, violence, chronic respiratory disease, cardiovascular disease or senility, which are not within the definition or scope for maternal death.Review meetings for cause analysis identified deficit in data that results in difficulty in assigning cause of death and inadequate use of ICD-10 coding (28). There were missing data related to verbal and social autopsies. These activities include a travel cost while there is no provision of conveyance allowances for health workers involved in the MPDSR program (17).

Both facility and community: At the level of both community and facility, barriers included inadequate supply of logistics (11), tendency of blaming healthcare providers present during the maternal and perinatal deaths) (12), lack of HR capacity (15) (11), deficiencies in local level action plan (19), lack of refresher training (17), high turnover of human resources (11) and divisional cause-analysis workshops not being conducted as per schedule (26). Moreover, action plans were neither developed nor implemented at local level (19). Therefore, local level strategies and responses to mitigate maternal and perinatal deaths were not adequate (4).

National level: At the national level, national MPDSR committee meeting not held at a regular basis (26), limited monitoring and supervision of the program (10) and inadequate coordination between health and family planning department swere the note worthy barriers.

Table 3: The enablers and barriers of MPDSR implementation in Bangladesh

Level	Key Enablers	Key Barriers
Community level	• Aware and engaged community (engaged grassroots) • High level of commitment of Community Health Workers • Support from community organizations/ local NGOs • Good infrastructure development in previously hard-to-reach areas	• Underreporting of deaths • Delay in death notification (DN) • Delay in conducting VA and inadequacy in identifying the cause of death • Misinformation • Lack of cause analysis at the local level • No provision for conveyance allowances for health workers • Lack of social action in the community • Gender issues (predominantly male community health workers) in the MPDSR steps
Facility level	• Trained and skilled staff • Involvement of interdisciplinary teams	• Review meetings not conducted as scheduled • Staff assigned to MPDSR are overworked
Data flow	• MPDSR data available in DHIS-2 platform helps in informed decision-making and action plans by healthcare managers	• Server issues/ difficulties in data entry • Lack of separate database for MPDSR • Error in data entry • Inadequate use of ICD-10 coding • No coordination between the national Civil Registration and Vital Statistics and the MPDSR data
Both facility and community	• Culture of trust and coordination • Use and follow-up of Action Plan • Active engagement of focal person • Organized supervision and monitoring	• Inadequate supply of logistics • Blame-game (Tendency of blaming healthcare providers present during the maternal and perinatal deaths) • Lack of HR capacity • Deficiencies in local level Action Plan • Lack of refresher training • High turnover of human resources • Divisional cause-analysis workshop not conducted at a regular basis
National level	• Presence of a robust national MPDSR framework and guideline • Regular monitoring and supervision through video surveillance by QIS • Regular implementation of national-level TOTs organized • Incorporating MPDSR into national maternal and neonatal health-related policies and OP • Laws-in-progress to ensure death notification • High level of commitment from the government	• National MPDSR committee meeting not held at a regular basis • Limited monitoring and supervision of the program • Lack of coordination between health and family planning departments

IV. DISCUSSION

The current scoping review identified the successes in developing an evidence-based framework with well-defined guidelines for implementation of MPDSR as a national program since 2016 till date in Bangladesh. The evidence gathered included successes as well as challenges in implementation. The enablers and barriers in program implementation were also identified and summarized for informing the program

improvement activities. Thereview identified a number of challenges in implementation. The maternal and neonatal deaths were not reported properly, timely or sometimes death notification was delayed; health workers working at the field level were not provided financial support for conveyance required during the various stepsof MPDSR implementation. There were inadequate human resources and logistics, irregularity in conducting review meetings for cause analysis, lack of monitoring and supervision of program activities. We have discussed the barriers and enablers of MPDSR in this review paper. The goal was to understand thestrengths of the current program to overcome the existing barriers of MPDSR scale-up in Bangladesh.

Despite the reduction in maternal and neonatal deaths over the last two decades, disparities still remain between the high-income and low-and-middle income countries with 99% of maternal deaths occurred in LMICs (17, 32). To reduce this high burden of maternal mortality, most countries with context similar to Bangladesh have implemented a system for reporting and responding to maternal and perinatal deaths, though the nomenclatures and terminologies may slightly differ.

Based on the successful experience of piloting MPDSR in Thakurgaon in 2010, and subsequent expansion in 10 districts of Bangladesh between 2011 and 2015, the acceptability of the program to the community, healthcare providers, and other stakeholders were high (1, 24). Evidence of reduced maternal and neonatal deaths at the local level compelled the government to go forth with a nationwide scale-up starting in 2016. In 2019, DGHS included 16 districts for implementation and 22 districts in the year 2020. MPDSR is now covering 50 districts. UNICEF, UNFPA, Save the Children, WHO and other development partners are supporting the implementation (1, 24).

A study conducted in five South East Asian countries reported that Sri Lanka has an well-structured MPDSR system (17). The mainstay in success was the strength of the health system, coordination and leadership at local level. In Sri Lanka, maternal deaths has been made notifiable since 1985 within a nation-wide surveillance system and data is shared with CRVS in order to avoid duplication and ensure the accuracy of the data (17). Similarly, Bangladesh has taken the initiative to coordinate MPDSR with CRVS to ensure death registration.

Despite robust guidelines, several barriers were seenat the level of implementation, such as limited number and capacity of human resources and a lack of motivation among staff. An assessment on MPDSR implementation in four sub-Saharan countries: Nigeria, Rwanda, Tanzania and Zimbabwe also identified similar barriers and enablers in implementation (12).

Some of the enablers identified in sub-Saharan countries include interdisciplinary teamwork, good communication among staff and support at both national and subnational levels(10, 11, 12) which have been documented in the current review regarding MPDSR in Bangladesh.

Causal analysis is difficult if data from death review is deficit as documented in implementation experiences in Bangladesh (24). Similar factors were reported in a field action study in Kenya (14). The report further identified that in Kenya underreporting of maternal deaths led to a lower than actual estimate of maternal mortality ration. Only half of the deaths identified were reviewed and the reviewers had difficulties assessing the cause of death, due to lack of proper documentation. Moreover, the resulting actions or responses were limited (14).

Although Bangladesh has made remarkable progress in reducing maternal and neonatal deaths, there are lessons to be learned from countries with a similar context. Bangladesh can learn from the program experiences of Sri Lanka, where maternal death reporting system is linked to the CRVS (17). Moreover, the coordinated effort to report facility deaths and community deaths along with mandatory death review meetings and wide dissemination of causes of death, has reinforced the success of the program in Sri Lanka (17). Based on the findings of our study,

policymakers and stakeholders can make informed decisions for supporting the scale-up of MPDSR in Bangladesh.

To our knowledge, this is the first scoping review on MPDSR conducted in Bangladesh. Our scoping review is comprehensive in the inclusion of guidelines, program reports and grey literature through consultation with experts of MPDSR implementation in Bangladesh. However, our study has few limitations: despite our attempt to capture all relevant information related to MPDSR in Bangladesh, some relevant literature may have been missed in the search. Our inclusion criteria excluded obstetric inquiries, confidential inquires and maternal near-miss reviews. The majority of MPDSR-related literature report the outcomes of the intervention rather than documenting the enablers and barriers of the implementation process. Future scoping reviews could look into the outcomes of MPDSR implementation in both developed and developing countries. Further, it would be useful to analyze and program data with outcomes of MPDSR implementation in Bangladesh to understand the progress of the program.

V. CONCLUSION

The current scoping review generated evidence to understand the process of MPDSR implementation in Bangladesh, the current barriers and enablers of the program. Robust national guideline, central and community- level data entry allows death reporting at the field level and informed action at the policy level. The details of the steps involved in the process of implementation are crucial in understanding where bottlenecks exist and what can be done for overcoming them. These steps will be effective in sensitizing policymakers about the current obstacles in the MPDSR process and suggest recommendations for future improvement.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have provided consent for publication of this article.

Availability of data and materials:

The data we used in this manuscript can be made available upon request to researchers via Abu Sayeed Abdullah (sayeedciprb@gmail.com)

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Authors' contributions

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The Benefits of Neuromuscular Electrical Stimulation on Peripheral Muscular Strength Gain in Critical Patients in the Intensive Care Unit: A Literature Review

Jessica Mariana Silva dos Santos, Denilson da Silva Veras & Adria Yared Sadala

ABSTRACT

Introduction: The loss of muscle mass is a common problem associated with adult patients who stay in the ICU, this problem is considerably greater than in all other patient populations. Objective: This study aimed to investigate the use of neuromuscular electrical stimulation (NMES) in peripheral strength gain in critically ill patients admitted to the intensive care unit. Methodology: This is an exploratory, descriptive research that uses an integrative literature review, as a way of collecting data in search of scientific articles, books, periodicals, theses. The searches for articles in magazines was carried out in the following databases: Scientific Eletronic Library Online (SCIELO), Medical Literature Analysis and Retrieval System (MEDLINE), Physiotherapy Evidence Database (PeDRO).

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The Benefits of Neuromuscular Electrical Stimulation on Peripheral Muscular Strength Gain in Critical Patients in the Intensive Care Unit: A Literature Review

Os Beneficios Da Estimulação Elétrica Neuromuscular No Ganho De Força Muscular Periférica Em Pacientes Críticos Internados Na Unidade De Terapia Intensiva

Jessica Mariana Silva dos Santos[α], Denilson da Silva Veras[σ] & Adria Yared Sadala[ρ]

RESUMO

Introdução: A perda de massa muscular é um problema comum associado a pacientes adultos que ficam internados na UTI, tal problema é consideralmente maior do que em todas as outras populações de pacientes.

Objetivo: Esse estudo teve como objetivo investigar o uso da estimulação elétrica neuromuscular (ENMS) no ganho de força periférica em pacientes críticos internados na unidade de terapia intensiva.

Metodologia: Trata-se de uma pesquisa de caráter exploratório, descritivo e que se vale da revisão integrativa da literatura, como forma de coleta de dados em busca de artigos cientificos, livros, periodicos, teses. As buscas dos artigos em revistas eletrônicas foi realizada nas seguintes base de dados:

Scientific Eletronic Library Online (SCIELO), Medical Literatura Analysis and Retrieval System (MEDLINE), Physiotherapy Evidence Database (PeDRO).

Resultados: Observou-se através das pesquisas que a estimulação elétrica neuromuscular associada com outros recursos e técnicas teve bons resultados em relação a ganho de força muscular em pacientes críticos internados na UTI.

Conclusão: O uso da ENMS em unidade de terapia intensiva é uma medida que se mostrou eficaz para o ganho de força muscular em pacientes criticos internados na UTI, pois está associada a cuidados dos fisioterapeutas presentes e outras técnicas que ajudaram muito na recuperação de muitos pacientes criticos na UTI.

Palavras-Chave: Terapia por estimulação elétrica, unidade de terapia intensiva, força muscular, fisioterapia.

ABSTRACT

Introduction: The loss of muscle mass is a common problem associated with adult patients who stay in the ICU, this problem is considerably greater than in all other patient populations. Objective: This study aimed to investigate the use of neuromuscular electrical stimulation (NMES) in peripheral strength gain in critically ill patients admitted to the intensive care unit. Methodology: This is an exploratory, descriptive research that uses an integrative literature review, as a way of collecting data in search of scientific articles, books, periodicals, theses. The searches for articles in magazines was carried out in the following databases: Scientific Eletronic Library Online (SCIELO), Medical Literature Analysis and Retrieval System (MEDLINE), Physiotherapy Evidence Database (PeDRO).

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Results: It was observed through research that electrical stimulation neuromuscular function associated with other resources and techniques has had good results regarding muscle strength in critically ill patients admitted to the ICU.

Conclusion: The use of NMES in a unit intensive care is a measure that has been shown to be effective in gaining muscle strength in critical patients who were already in the ICU for a long time, as it is associated with care physiotherapists present and other techniques that helped a lot in the recovery of many critical patients in the ICU.

Keywords: electric stimulation therapy, unit intensive care, muscle strength, physiotherapy.

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I. INTRODUÇÃO

Tem sido mostrado de forma consistente que repouso no leito, descarga de membro e/ou imobilização induz atrofia muscular com uma perda de massa muscular inicial de 3-11% nas primeiras duas a três semanas desde o inicio da imobilização (MEESEN et al, 2010). Á medida que mais pacientes sobrevivem á doença aguda, complicações a longo prazo se tornam mais aparentes, possivelmente levando a maior deficiência, com estadias e reabilitações prolongadas em cuidados intensivos (FERREIRA; VANDERLEI; VALENTI, 2013). Modalidades terapêuticas invasivas, como ventilação mecânica, suporte circulatório, uso de agentes sedativos, bloqueadores neuromusculares, corticosteroides ou certos antibióticos afetará negativamente na massa muscular e força (SEGERS et al, 2014). A estimulação elétrica neuromuscular (NMES) embora não seja uma rotina como parte da terapia, demonstrou ter um efeito benéfico na preservação de massa muscular e força em indivíduos saudáveis imobilizados e em populações com doenças crônicas. (PARRY et al, 2013).

Fraqueza muscular é definida como um déficit bilateral de força muscular em todos os membros, que é acompanhado por uma perda profunda de massa muscular, está associada ao desmame retardado da ventilação mecânica e a permanência prolongado na UTI (MAFFIULETTI et al, 2013). Os pacientes apresentam diferentes graus de fraqueza muscular dos membros que também envolvem os músculos respiratórios e são dependentes do ventilador (LATRONICO; GOSSELINK, 2015)

Uma fraqueza muscular do paciente crítico apresenta-se de forma difusa e simétrica, acometendo a musculatura estriada esquelética apendicular e axial. Os grupos musculares proximais geralmente são mais afetados que os músculos distais, com variável envolvimento dos reflexos tendinosos profundos e da inervação sensório-motora (PINHEIRO; CHRISTOFO-LETTI, 2012). Esses distúrbios musculares podem ter um impacto negativo sobre os pacientes como falta de independência e qualidade de vida, bem como sua capacidade funcional após alta hospitalar (SACHETTI et al, 2018).

A estimulação elétrica neuromuscular (NMES) foi identificado como uma alternativa ao exercício ativo em pacientes gravemente doentes. NMES é um método não invasivo que estimula o músculo sem participação ativa, que pode manter a função do músculo esquelético. NMES tem sido usado na reabilitação de lesões esportivas e como meio de prevenção muscular em pacientes imobilizados (WILLIAMS; FLYNN, 2013). O objetivo da NMES em estados de doenças avançadas é prevenir ou reverter a perda de massa muscular esquelética em pessoas que não são capazes de praticar exercícios (NUSSBAUM et al, 2017).

A estimulação elétrica neuromuscular (NMES) tem sido usada em uma variedade de populações clínicas, particularmente em pacientes que são incapazes de participar de atividades voluntárias (programas de exercícios). Tem se mostrado benéfico em pacientes com doenças crônicas, doença pulmonar obstrutiva (DPOC) e

insuficiência cardíaca crônica (ICC). Recentemente, a estimulação elétrica neuromuscular dos membros inferiores foi bem sucedida e descrita como um método de treinamento alternativo útil para aumentar a força de quadríceps femoral, melhorando a tolerância ao caminhar e qualidade de vida em pacientes com a DPOC (MEKKI et al, 2018).

Publicações recentes avaliaram seu efeito sistêmico em populações saudáveis e pacientes criticamente enfermos, incluindo pacientes em UTI e mostraram sua potencial eficácia na prevenção de UTI ou fatores relacionados (PATSAKI et al, 2017).

A EENM percutânea tornou-se um método clinicamente estabelecido para induzir o crescimento muscular, bem como aumentar a força e a resistência, portanto, poderia ser uma maneira promissora de prevenir perda de massa muscular (GRUTHER et al, 2010). Uma recente revisão sistemática mostrou que o NMES combinado com o cuidado usual provou ser mais eficaz do que o cuidado usual sozinho para prevenir a fraqueza do músculo esquelético em casos de pacientes gravemente enfermos (SANTOS et al, 2018).

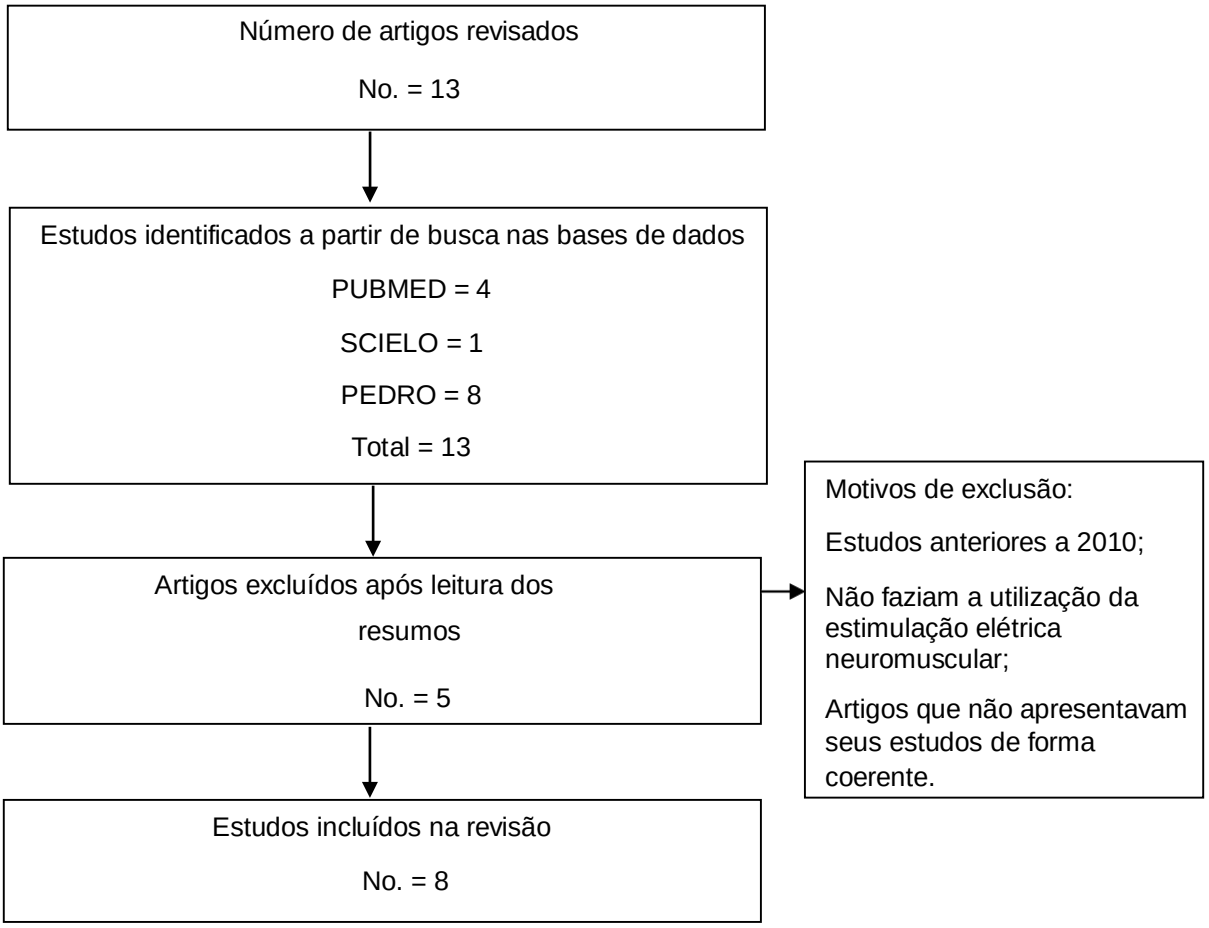
Dentro desse contexto o objetivo deste estudo foi analisar os benefícios da estimulação elétrica neuromuscular no ganho de força muscular periférica em pacientes críticos internados na UTI.

II. METODOLOGIA

O presente estudo constituiu-se em uma pesquisa de caráter bibliográfico e que se vale da Revisão Integrativa da Literatura dirigida especificamente aos trabalhos que apresentavam relatos sobre os beneficios da estimulação elétrica neuromuscular no ganho de força muscular periférica em pacientes criticos internados na UTI. Foram incluídos artigos onde relatavam pacientes criticos internados na unidade de terapia intesiva (UTI) e devido a um período de tempo acamados estavam perdendo massa e força muscular. Foram excluídos artigos anteriores a 2010 que não faziam uso da estimulação elétrica neuromuscular e que não apresentavam seus resultados de forma coerente.

O presente estudo foi realizado através de pesquisas em bases de dados: Scientific Eletronic Library Online (SCIELO), Medical Literatura Analysis and Retrieval System Online (MEDLINE), Base de Dados em Evidências em Fisioterapia (PEDro) revistas e artigos atualizados. Foi feita uma seleção de 13 artigos, utilizando os descritos: eletroestimulação neuromuscular, unidade de terapia intensiva, paciente adulto, modalidade de fisioterapia. O período da pesquisa foi compreendido entre os anos de 2010 a 2020 onde conteve apenas artigos que correspondiam ao interesse da pesquisa proposta.

Os artigos foram selecionados através de uma pesquisa e leitura minuciosa, havendo uma avaliação de todo o conteúdo que foi abordado. A seguir o fluxograma, demonstra o processo metodológico da revisão integrativa da literatura, evidenciando todos os passos da presente pesquisa.



Fonte: Autora, 2020

III. RESULTADOS E DISCUSSÃO

O presente estudo inclui 08 artigos que preenchiam os critérios de inclusão como podemos observar no quadro a seguir:

Quantidade	Autor/Ano	Título	Tipo de Estudo	Revista	Resultados
1	MAFFIU LETTI et al, 2013	Neuromuscular lectrical stimulation for preventing skeletal- muscle weakness and wasting in critically ill patients: a systematic review	Revisão Sistemática	BMC Medicine	A NMES adicionada ao cuidado usual provou ser mais eficaz do que o cuidado usual sozinho para prevenir fraqueza do músculo esquelético em pacientes criticamente enfermos. No entanto, há evidências inconclusivas de seu beneficio em prevenção de perda muscular.

2	PINHEIRO; CHRISTOFOLETTI, 2012	Fisioterapia motora em pacientes internados na unidade de terapia intensiva: uma revisão sistemática	Revisão sistemática	Revista Brasileira de Terapia Intensiva	A fisioterapia motora consiste em uma terapia segura e viável em pacientes críticos, podendo minimizar os efeitos deletérios da imobilização prolongada. A abordagem Envolvendo eletroestimulação, cicloergômetro e cinesioterapia motora mostrou respostas positivas no paciente sob terapia intensiva.
3	MEESEN et al, 2010	Neuromuscular electrical stimulation as a possible means to prevent muscle tissue wasting in artificially ventilated and sedated patients in intensive care unit: a pilot study	Estudo piloto	Neuromodulation Journal	A atrofia muscular é evitada por estimulação elétrica neuromuscular intermitente enquanto esta intervenção não mostrou nenhum impacto óbvio nas condições cardiorrespiratória s dos pacientes.
4	SEGERS et al, 2014	Feasibility of neuromuscular electrical stimulation in critically ill patients	Estudo observacional	Journal of Critical Care	Pacientes criticamente enfermos com sepse, edema ou recebendo vasopressores eram menos propensos a responder a NMES com uma contração adequada do quadríceps. A estimulação elétrica neuromuscular é uma intervenção segura para ser administrada na UTI.
5	WILLIAMS; FLYNN, 2013	A review of the efficacy of neuromuscular electrical stimulation in critically ill patients	Revisão sistemática	Informa Healthcare	Os designs dos estudos mostram que as evidências não são conclusivas, o que torna difícil tirar conclusões robustas sobre a eficácia da NMES em populações de pacientes em estado crítico.
6	KARATZANOS et al, 2012	Electrical muscle stimulation: an effect form of exercise and early mobilization to preserve muscle strength in critically ill patients	Estudo clinico	Critical Care Research and Practice	O exercício MNES induz efeitos benéficos na força muscular de pacientes de UTI. Esses efeitos dizem respeito principalmente a grupos musculares estimulados diretamente, mas também há evidências de efeitos em grupos musculares não estimulados.

7	MEKKI et al, 2018	Effect of adding neuromuscular electrical stimulation training to pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: randomized clinical trial	Ensaio clinico randomizado	Clinical Rehabilitat ion	A estimulação elétrica neuromuscular somada ao grupo de reabilitação pulmonar beneficiou-se de melhor tolerância à caminhada e melhora do equilíbrio do que só a reabilitação pulmonar.
8	GRUTHER et al, 2010	Effects of neuromuscular electrical stimulation on muscle layer thickness of knee extensor muscles in intensive care unit patients: a pilot study	Estudo piloto ramdomizado	Journal of Rehabilitat ion Medical	A estimulação elétrica neuromuscular aparece paraser um complemento útil para reverter a perda muscular em pacientes de longa permanência em unidades de cuidados (UTI); no entanto, estudos com um tamanho de amostra maior são n ecessários para confirmar essas promessas.

Fonte: Autora, 2020

Na revisão sistématica realizado por MAFFIULETTI et al., (2013), foram avaliados 8 estudos elegíveis envolvendo 172 pacientes. A qualidade metodológica dos estudos foi de moderado a alto. Cinco estudos relataram um aumento na força ou melhor preservação da massa muscular com NMES, em um estudo de grande tamanho. Dois estudos encontraram melhor preservação da massa muscular com NMES, com tamanho de efeitos moderados. No entanto, há evidências inconclusivas de seu benefício em prevenção da perda muscular.

Na revisão sistemática realizada por PINHEIRO; CHRISTOFOLETTI., (2012), realizou-se uma análise inicial de 67 artigos potencialmente relevantes, apenas 8 contemplaram os critérios de seleção e abordaram os desfechos provenientes das técnicas de eletroestimulação, ciclo ergômetro e cinesioterapia. O tamanho amostral variou de 8 a 101 sujeitos, com média de idade entre 52 e 79 anos. Todos os pacientes estavam sob ventilação mecânica invasiva. Dos artigos analisados, seis indicaram benefícios significativos da fisioterapia motora em pacientes críticos, como melhora na força muscular periférica, capacidade respiratória e na funcionalidade.

No estudo piloto realizado por MEESEN et al., (2010), avalio-se 25 pacientes com idades entre 13 e 67 anos. Os pacientes foram hospitalizados para pós-operatório de cirurgia de revascularização do miocárdio, DPOC, insuficiência ventilatória ou AVC agudo, e foram divididos em grupo de intervenção e grupo controle. O grupo de intervenção foi submetido a treinamento diário de 30 minutos com NMES intermitente aplicado ao músculo quadríceps direito. Frequência cardíaca, frequência respiratória, pressão arterial sistólica e diastólica e saturação do oxigênio foram monitorados antes, durante e após a NMES. A circunferência de ambas as coxas foi medida. A intervenção resultou em uma redução significativa da atrofia muscular no membro estimulado em comparação com o membro não estimulado, sem causar impacto nas características cardiovasculares, respiratórias e hemodinâmicas.

No estudo observacional realizado por SEGERS et a., (2014), foram avaliados 50 pacientes com um prognóstico de permanência prolongada de pelo menos 6 dias na UTI. Houve realização de 25 minutos de NMES bilateral simultânea do músculo quadríceps femoral. Esta estimulação foi

realizada 5 dias na semana. O resultado foi que em 50% dos pacientes, uma contração adequada do quadríceps foi obtida em pelo menos 75% das sessões de NMES. Pacientes responderam melhor para a NMES no início da permanência na UTI. Pacientes com sepse, edema ou recebendo vasopressores eram menos propensos a responder a NMES com uma contração adequada do quadríceps.

Na revisão sistemática realizada por WILLIAMS; FLYNN,. (2013), avaliou-se 8 artigos através de um programa de avaliação e competências. Dois dos estudos da revisão relataram os efeitos sistêmicos de NMES onde relataram significativo aumento nas taxas de repercussão e aumento da pressão sistólica e frequência cardíaca. Em todos os pacientes após NMES se identificou que estava ocorrendo um efeito sistólico. Cinco dos estudos relataram os efeitos do NMES na massa muscular. No entanto, eles relataram dificuldades de edema tecidual e só encontraram diferenças significativas quando esses pacientes foram excluídos da análise. Dois dos estudos usaram medidas de força muscular em membros superiores e inferiores para avaliar o efeito de NMES usando a pontuação do Conselho de Pesquisa Médica (MRC). Eles relataram menor duração da ventilação mecânica, diminuiu tempo de desmame de longo prazo, maior número de dias sem ventilação e menor tempo de permanência na UTI no grupo de NMES. No entanto, a heterogeneidade nos projetos de estudo tornou difícil comparar os resultados dos estudos.

No estudo clinico realizado por KARATZANOS et al., (2012), onde participaram desse estudo 142 pacientes consecutivos com idade maior de 18 anos, com APACHE II, pontuação ≥ 13, foram atribuídos aleatoriamente ao grupo NMES ou ao grupo controle. Sessões de NMES foram aplicadas diariamente no vasto lateral, vasto medial e fibular longo de ambas as extremidades inferiores. Vários grupos musculares foram avaliados com o Conselho de Pesquisa Médica (MRC) escala para força muscular. 24 pacientes no grupo NMES e 28 pacientes do grupo controle foram finalmente avaliados. Foi concluído que a NMES tem efeitos benéficos na força de pacientes criticamente enfermos, afetando principalmente os grupos musculares estimulados, embora também possa afetar grupos musculares não envolvidos, apresentando-se como um meio potencial eficaz na preservação de força muscular e mobilização precoce nesta população de pacientes.

No ensaio clinico randomizado realizado por MEKKI et al., (2018), um total de 45 pacientes com DPOC foram atribuídos 25 ao grupo de intervenção e 20 ao grupo controle. O grupo de intervenção foi submetido a uma estimulação elétrica neuromuscular adicionada a reabilitação pulmonar, e o grupo controle foi submetido apenas a reabilitação pulmonar, três vezes por semana durante seis meses. Uma plataforma estabilométrica, teste de time up and go, testes de escala de equilíbrio de Berg, teste de caminhada de 6 minutos e o máximo de contração voluntária foram medidos. Foi concluído que a NMES somada ao grupo de reabilitação pulmonar beneficiou-se de melhor tolerância a caminhada e melhora do equilíbrio do que a única reabilitação pulmonar.

No estudo piloto realizado por GRUTHER et al., (2010), foram selecionados 33 pacientes homens e mulheres com idade média de 55 anos. Foram estratificados (com base no tempo de permanência no hospital) em 2 grupos: 17 pacientes agudos (< 7 dias) e 16 pacientes de longo prazo (> 14 dias). Ambos os grupos foram randomizados para um grupo de estimulação ou em grupo de simulação de estimulação. NMES foi aplicada aos músculos extensores do joelho por um período de 4 semanas (tempo de sessão 30-60 minutos, 5 dias/semana). As medições de ultrassom foram realizadas antes e depois do período de estimulação para quantificar a espessura da camada muscular de músculos extensores de joelho. Foi concluído que a NMES aparece para ser um complemento útil para reverter a perda muscular em pacientes de longa permanência na UTI, no entanto, estudos com um tamanho de amostras grande são necessários para confirmar essas promessas.

IV. CONCLUSÃO

O estudo possibilitou demonstrar os benefícios da estimulação elétrica neuromuscular (NMES) para ganho de força em pacientes críticos internados nas unidades de terapia intensiva. A NMES demonstrou ser um aliado importante aos fisioterapeutas nas unidades de terapia intensiva, pois ele associado a outros recursos e técnicas como: cinesioterapia motora, treino de

equilíbrio, uso do ciclo ergômetro ajudaram a pacientes críticos que estavam perdendo força muscular a conseguirem preservar e manter o seu ganho muscular.

Diante disso, notou-se no estudo que a NMES ajuda no combate a perda muscular em pacientes críticos internados em UTI. No entanto, novas pesquisas clinicas não bibliográficas precisam ser realizadas para comprovação de tais achados.

VI. DEDICATÓRIA

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Anticoagulation in a Patient with Lemierre Syndrome and Pulmonary Septic Embolisms

María José Rivas, Kevin D'elía, Ignacio Bianconi & Paola Novelli Poisson

ABSTRACT

Lemierre's syndrome, also called septic thrombo phlebitis of the internal jugular vein, necrobacillosis or postanginal sepsis, is an infection that begins in the oropharyngeal space, is complicated by septic throm bophlebitis of the internal jugular vein and infectious metastases. The rapid progression to serious clinical conditions that compromise the patient's life and its low frequency justify the disclosure of clinical cases. We present the case of a 27-year-old woman who de veloped facial edema and trismus 48 hours after com pleting treatment with phenoxymethylpenicillin for an odontogenic infection. An angio-CT of the craniofacial massif revealed an extensive thrombus in the internal jugular vein and a computed tomography of the chest showed septic pulmonary emboli. Treatment consisted of broad-spectrum intravenous antibiotics and early anticoagulation.

Keywords: oropharyngeal, septic thrombophle-bitis of the internal juyugal vein, septic emboli, Lemierre's syndrome.

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Anticoagulation in a Patient with Lemierre Syndrome and Pulmonary Septic Embolisms

Anticoagulación en Paciente Con Síndrome De Lemierre Y Mbolias Sépticas Pulmonares

María José Rivas[α], Kevin D'elía[σ], Ignacio Bianconi[ρ] & Paola Novelli Poisson[Ω]

RESUMEN

El síndrome de Lemierre, también denominado trom boflebitis séptica de la vena yugular interna, necrobaci losis o sepsis postanginal es una infección que inicia en el espacio orofaríngeo, se complica con tromboflebitis séptica de la vena yugular interna y metástasis infeccio sas. La rápida progresión a cuadros clínicos graves que comprometen la vida del paciente y su baja frecuencia justifican la divulgación de casos clínicos. Se presenta el caso de una mujer de 27 años de edad, que a las 48 horas de completar el tratamiento con fenoximetilpenicilina por una infección odontógena evolucionó con edema facial y trismus. En la angio-TC de macizo craneofacial se evidenció extenso trombo en la vena yugular interna y en la tomografía computarizada de tórax, embolias sépticas pulmonares. El tratamiento consistió en antibió ticos endovenosos de amplio espectro y anticoagulación de manera precoz.

Palabras Clave: orofaringe, tromboflebitis séptica de vena yugular interna, embolias sépticas, síndrome de lemierre.

ABSTRACT

Lemierre's syndrome, also called septic thrombo phlebitis of the internal jugular vein, necrobacillosis or postanginal sepsis, is an infection that begins in the oropharyngeal space, is complicated by septic throm bophlebitis of the internal jugular vein and infectious metastases. The rapid progression to serious clinical conditions that compromise the patient's life and its low frequency justify the disclosure of clinical cases. We present the case of a 27-year-old woman who de veloped facial edema and trismus 48 hours after com pleting treatment with phenoxymethylpenicillin for an odontogenic infection. An angio-CT of the craniofacial massif revealed an extensive thrombus in the internal jugular vein and a computed tomography of the chest showed septic pulmonary emboli. Treatment consisted of broad-spectrum intravenous antibiotics and early anticoagulation.

Keywords: oropharyngeal, septic thrombophle-bitis of the internal juyugal vein, septic emboli, Lemierre's syndrome.

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I. INTRODUCTION

El síndrome de Lemierre es una rara condi ción que afecta principalmente a adultos jóve nes sin antecedentes patológicos relevantes. Fue descrito en 1936 por Andrés Lemierre en una serie de 20 casos de sepsis post faringitis a gérmenes anaerobios[1].Inicia como una infec ción bacteriana en orofaringe, y luego de una a dos semanas se complica con una trombofle bitis séptica de la vena yugular interna. Estas infecciones del espacio cervical profundo se han vuelto poco comunes posterior al uso de antibióticos, sin embargo, cuando se presentan tienen un inicio rápido y pueden progres a complicaciones potencialmente mortales como las embolias sépticas[2,3].

En una búsqueda bibliográfica realizada en la Biblioteca Nacional de Medicina de EE.UU. a través de PubMed mediante los términos

("Lemierre Syndrome"[Mesh]) AND ("Case Reports" [Publication Type]) hemos encontrado solo 306 reportes de casos publicados hasta el 1 de agosto del 2022. Se estima una frecuencia de un caso por millón de habitantes anualmente[4].

1.1 Caso Clínico

Mujer de 27 años, con antecedentes de asma no con trolada, infección leve por SARS-CoV-2. En marzo del 2021 consultó a guardia médica por dolor en hemicara izquier da y trismus. Refirió haber completado 48 horas antes el tratamiento antibiótico con fenoximetilpenicilina 1 000 000 UI diaria vía oral, durante cinco días, por flemón pe riamigdalino.

Al examen físico de ingreso se encontraba hemodiná micamente estable, sin requerimiento de oxígeno com plementario, y sin hallazgos de relevancia en la semiolo gía respiratoria. Al examen de cabeza y cuello se observóen hemicara izquierda edema blando, doloroso, adeno megalias cervicales palpables y dolorosas, a predominio homolateral y trismus.

Se hicieron estudios complementarios. El laboratorio de ingreso informó leucocitosis, plaquetopenia, aumen to de reactantes de fase aguda y el resto de los paráme tros dentro de valores normales. Se realizó angio-TC de macizo craneofacial (Fig. 1) donde se evidenció extenso trombo en carótida interna y externa. Se completaron los estudios con una tomografía de tórax y ecografía Doppler arterial de vasos del cuello sin hallazgo de re levancia.

Se inició de manera precoz tratamiento antibiótico endovenoso con ceftriaxona 1 g cada 12 horas, clindami cina 300 mg cada 6 horas y anticoagulación con enoxa parina ajustado a peso y función renal, 60 mg subcutá neo cada 12 horas. Evolucionó a las 72 horas de haber iniciado tratamiento dirigido, con fiebre de 38.5 °C y aumento de leucocitosis, por lo que se realizaron nue vos estudios complementarios, entre ellos un ecocardio grama Doppler sin hallazgo de vegetaciones cardiacas y TC de tórax donde se evidenciaron embolias sépticas pulmonares bilaterales (Fig. 2). Con los hemocultivos de ingreso cerrados negativos, se decidió nueva toma de hemocultivos por 3 unidades, cultivo de exudado faríngeo y se rotó ceftriaxona a piperacilina tazobactam 4.5 g cada 6 horas endovenoso.

La paciente evolucionó favorablemente, sin rescate de gérmenes en cultivos. A los 14 días de iniciado el nuevo esquema terapéutico, y con TC de tórax control sin le siones pulmonares se decidió continuar tratamiento an tibiótico con clindamicina vía oral 300 mg cada 6 horas, anticoagulación con acenocumarol ajustado a peso cor poral y egreso hospitalario.

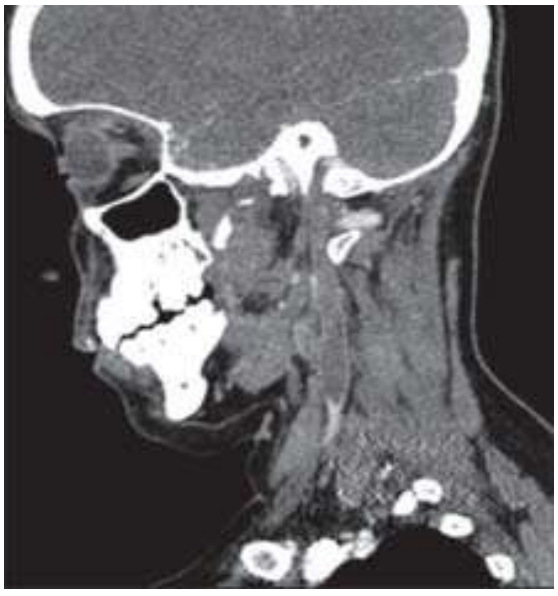

Figura 1: Corte sagital de angio TC de macizo craneofacial donde se observa extenso trombo en la vena yugular interna

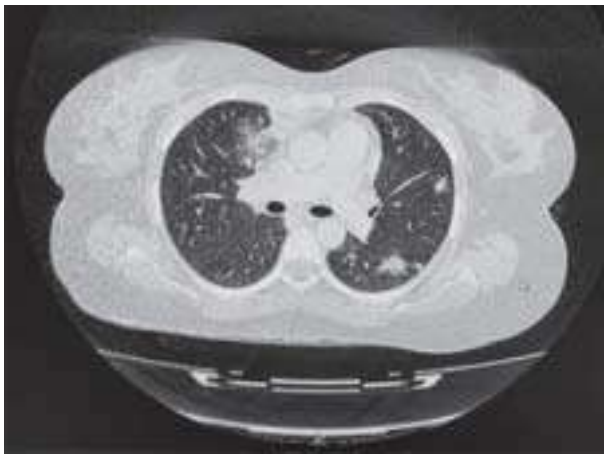

Figura 2: Corte axial de tomografía de tórax donde se observan opacidades nodulares bilaterales compatibles con embolias sépticas

II. DISCUSIÓN

La tromboflebitis de la vena yugular interna es una afección infrecuente, que ocurre preva lentemente en adultos jóvenes y sanos. Es cau sada por flora habitual de las superficies muco sas contiguas a partir de las cuales se originó la infección. El patógeno más común es el *Fusobac terium necrophorum*[4, 5]. En la mayoría de los casos, la infección primaria consiste en afectación de amígdalas palatinas o del tejido periamigdalino, continúa con invasión local al espacio faríngeo y a la vena yugular interna. Los posibles meca nismos incluyen diseminación hematógena a través de la vena amigdalina, invasión periamig dalina o diseminación al espacio faríngeo lateral adyacente a través de los vasos linfáticos[2].

Clínicamente, este síndrome suele estar pre cedido una o dos semanas por faringitis, mas toiditis, otitis, infecciones dentales, abscesos faríngeos o mononucleosis infecciosa. Las ma nifestaciones clínicas pueden incluir fiebre, escalofríos, amigdalitis exudativa, odinofagia, disfagia, trismus, dolor de cuello unilateral y al teración de la sensibilidad. El tiempo entre el an tecedente de infección y la tromboflebitis suele ser de una semana[6].

El estudio de elección para el diagnóstico de trombo en la vena yugular interna es la angio-TC de cuello. También se puede utilizar la ecografía de vasos de cuello, y RMN de partes blandas[7, 8].

Los síntomas respiratorios reflejan una compli cación de la embolia pulmonar séptica que se pue den presentar como lesiones cavitarias necróticas, infiltrados, derrames pleurales, empiemas, neu motórax y mediastinitis necrotizante. Puede ocu rrir diseminación hematógena a otros sitios, con o sin descompensación clínica, debiendo descartar por su gravedad endocarditis infecciosa. Después de la afectación pulmonar, continúan en frecuen cia las grandes articulaciones (rodillas y caderas). Otras menos comunes son las lesiones cutáneas, osteomielitis, endocarditis y abscesos de tejidos blandos, esplénicos y hepáticos.

Los pilares del tratamiento incluyen la terapia antibiótica, así como considerar la necesidad de una intervención quirúrgica y anticoagulación. El rescate de gérmenes, ya sea en hemocultivos o cultivo de faringe no es lo más frecuente. La te rapia empírica para el síndrome de Lemierre clá sico debe apuntar a gérmenes anaerobios, como *F. necrophorum* y estreptococos orales. Los regíme nes antibióticos incluyen, piperacilina tazobac tam 4.5 gramos cada 6 horas endovenoso, car bapenem o ceftriaxona 2 gramos cada 24 horasmás metronidazol. En quienes presenten ines tabilidad hemodinámica u otros hallazgos que sugieran enfermedad grave, o factores de riesgo de infección por *Staphyloccocus aureus*, se debe incluir vancomicina endovenosa. Para pacientes con compromiso del sistema nervioso central, se debe utilizar un régimen de amplio espectro con penetración de la barrera hematoencefálica[9]. Una vez desarrollados los cultivos, debe ajustarse la terapia antibiótica dirigida al germen aislado. La terapia antimicrobiana efectiva requiere regíme

nes de al menos cuatro semanas de duración con dos semanas iniciales de terapia endovenosa. Se recomienda 6 a 8 semanas de tratamiento según las características clínicas del paciente. Una vez controlada la infección, las opciones orales para el tratamiento de la infección incluyen metroni dazol 500 mg cada 8 horas, amoxicilina clavuláni co 875/125 mg cada 12 horas o clindamicina 300 mg cada 6 horas.

En el contexto de bacteriemia persistente o de terioro clínico, se deberían realizar estudios por imágenes para evaluar extensión del trombo o presencia de colecciones que requieran drenaje.

Hay controversias en quienes pueden benefi ciarse con la anticoagulación. Quizás pueda ser útil en reducir la propagación de trombos o even tos embólicos sépticos que se originan a partir de la vena yugular. En la bibliografía revisada, las recomendaciones para iniciar anticoagulación son débiles, y está indicada si existe progresión de la trombosis, persistencia del cuadro febril o bacteriemia después de cinco días de tratamiento antimicrobiano apropiado[10-12]. En este caso, se de cidió en conjunto con el Servicio de Hematología iniciar anticoagulación temprana para disminuir las complicaciones mencionadas. La duración del tratamiento anticoagulante es incierta. Es acep table interrumpirla una vez que el paciente haya mejorado clínica e imagenológicamente.

En conclusión, la rápida progresión a cua dros clínicos graves que comprometen la vida del paciente, y su baja frecuencia justifican el reporte de estos casos clínicos. A pesar de que existan tratamientos antimicrobianos efecti vos, la evolución sigue siendo incierta debido a múltiples factores que inciden en ésta. Des cribir la evolución clínica del paciente con in dicaciones controversiales de anticoagulación permite identificar elementos claves para el desarrollo de futuras líneas de tratamiento e investigación.

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