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Clinical efficacy of implementing a Patient Blood Management (PBM) Protocol in joint replacement surgery: a retrospective cohort study in a national referral center

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Abstract. – OBJECTIVE: The aging of population has dramatically broadened the total number of Total Hip Arthroplasty (THA) and Total Knee Arthroplasty (TKA) performed worldwide. To optimize the number of blood transfusions performed, a multimodal and multidisciplinary approach was introduced, called Patient Blood Management (PBM). The aim of the present retrospective study is to evaluate the feasibility and clinical outcomes of a PBM protocol applied in a national referral center for joint replacement surgery.

PATIENTS AND METHODS: Clinical reports of 9,635 patients undergoing primary THA or TKA, from 2014 to 2019, were screened. The trends of hemoglobin value at admission and at day 4 after surgery were analyzed. Furthermore, the trend of blood bags' requests and blood transfusions was longitudinally evaluated to assess the efficacy of our PBM protocol and its potential impact in reducing the length of stay in the hospital.

RESULTS: In 2014, mean hemoglobin (Hb) levels at postoperative day 4 were 10.3 g/dl and 10.2 g/dl for TKA (unilateral and bilateral, respectively), and in 2019 were 11.3 g/dl and 11.6 g/dl (unilateral and bilateral, respectively, *p*=0.001). Total requested red blood cell (RBC) transfusions by each surgery over time have decreased for THA (277 in 2014 *vs.* 120 in 2019, *p*=0.001). A correlation matrix analysis between Hb level, body mass index (BMI), age, days spent in orthopedic (OR) ward and number of requested transfusions showed that RBC bags transfusions were related to the length of the hospital stay.

CONCLUSIONS: A timely application of a PBM protocol in the perioperative period of TKA and THA was significantly associated to the reduction of blood transfusions and total length of hospital stay, with clear benefits for both the patients and the hospital.

Key Words:
Osteoarthritis, Knee, Hip, Arthroplasty, Patient blood management, PBM, Blood transfusion.

Introduction

The increasingly ageing of the population and the improvements in healthcare standards dramatically broadened the total number of Total Hip Arthroplasty (THA) and Total Knee Arthroplasty (TKA) performed, esteemed to furtherly expand up to 2-fold, with presumed global incidence of 635,000 procedure for THA and 1.26 million for TKA by 2030[1].

Despite these procedures are nowadays considered solid and fortunate surgical techniques able to improve the quality of life, their association to a significant perioperative bleeding is undeniable, i.e., up to 1,000-1,500 ml for THA[2,3].

Post-operative anemia is often addressed with allogenic packed red blood cells (RBC) transfusion, whose effectiveness is counterbalanced by its scarcity and possible complications (infection, sepsis, increased mortality and morbidity), advising its application as the last resort[4-6].

Furthermore, in recent years, physicians began to partially shift the attention on the preoperative hemoglobin (Hb) concentration as well, since it

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is considered a predictive value of morbidity and mortality even before the operation[7-10]. According to a recent International Consensus Statement, anemia should be defined as Hb<13 g/dl in surgical cohorts, irrespective of gender and it should be outlined an independent predictive factor for perioperative RBC transfusions[11].

A retrospective study[12] conducted on Jehovah's Witness patients subjected to non-cardiac surgery, who negated to receive allogenic transfusions, evidenced an increased perioperative mortality in those who suffered from preoperative anemia. Although disparate causes of preoperative anemia have been investigated[13], the certainly most common denominator among anemic patients is the impaired iron status. Iron deficiency is dramatically prevalent among general population and its resolution before surgery expose the patient to a minor risk of experiencing postoperative anemia and blood transfusions as well[14].

A recent meta-analysis[13] of 21 trials in different clinical settings concluded that also non-anemic iron deficiency could be considered a mere disease since its relation to increased number of transfusions and postoperative complications. Moreover, a recent study[15] demonstrated how in surgical patients about to undergo surgery with an esteemed blood loss of 10% of total circulating blood, low iron store was associated to transfusions as well as in iron deficiency patients (ferritin below 30 μg/L), therefore they were treated and defined as comparable.

In addition, has been shown how the inflammatory status following the surgical trauma impairs the iron status regulation via interaction of interleukin-6, hepcidin and ferroportin, whose net effect is the inhibition of the gastrointestinal iron uptake, sequestration in macrophages and suppression of erythropoiesis[16].

Therefore, to accomplish the blood management optimization in a multilevel setting, a multimodal and multidisciplinary approach is mandatory, the Patient Blood Management (PBM).

This innovative approach aims to achieve and maintain adequate Hb level, minimize blood loss and improve anemia tolerance through managing eventual iron deficiency[17-20].

From 2014, the orthopedic facility of our national referral hospital applied a PBM protocol centered on a multidisciplinary approach to the patient performed 30 days before the surgery.

This retrospective study aims at evaluating whether the clinical application of a PBM protocol in a high-volume hospital could reduce blood transfusions and improve the outcome, defined as the Hb level at the fourth day, which is correlated to discharge from orthopedic department. As a secondary outcome we evaluated if restrictive transfusion policy could reduce blood request to the transfusion center.

Patients and Methods

Patients undergoing primary, cemented or cementless, THA or TKA were included in the present study. Patients affected by previous femoral fracture or undergoing revision surgery of the index limb were excluded. All the patients signed an informed consent for the use of their anonymized data for scientific purposes, and the Internal Review Board of IRCCS Humanitas Research Center approved the present retrospective study (ID No. 2315). The blood management protocol described below was fully applied to all patients as standard of care from 2016 to present. Our protocol consisted of three phases: (1) preoperative, (2) intraoperative, and (3) postoperative evaluation.

Preoperative Assessment

All the patients enrolled in the study, underwent a multidisciplinary team screening visit at least 30 days prior to surgery. Transversal competences including anesthesiologist, surgeon, internal medicine doctor and, if necessary, transfusion or antithrombotic experts were assorted during the same day.

The potential blood loss during the procedure was further assessed via a tailored single patient-based approach performed by surgeon and anesthesiologist.

Erythropoiesis optimization

Anemia, best defined as 'suboptimal Hb preoperative concentration', was diagnosed if Hb was below 13 g/dL[11]. Patients with anemia were studied for diagnosis and a prompt treatment was eventually commenced. Global iron status was investigated in all the patients, examining ferritin level, and C-reactive protein firstly, and potentially hemoglobin saturation to assess the effective iron deficiency. If ferritin was below 100 μg/L or transferrin saturation <30%, a timely treatment was started, according to the hospital protocol, with 1 g ferric carboxymaltose injection after a careful evaluation by a transfusion specialist doctor, otherwise a home therapy with oral iron supplements for one month[21,22] was administered.

Preoperative blood loss minimization

Analgesic therapy with non-steroidal anti-inflammatory drug (NSAID) was suspended just before surgery, supplementing the therapy with other pharmacological agents. An anamnestic-based evaluation of the thromboembolic risk throughout the Caprini score was carried out[23].

Optimization of physiological reserves for anemia tolerance

The multidisciplinary team completed a clinical and instrumental assessment to establish the grade of compensation in patients affected by chronic cardiopulmonary pathologies which could interfere with oxygen delivery.

Intra- And Peri-Operative Period

Blood loss restriction

Surgical procedures were performed from Monday to Friday, by the same orthopedic surgeons during the years considered. The anesthesiologic technique consisted in neuraxial regional anesthesia, with in intra-operative hypotension and a mean arterial blood pressure ^{3}60 mmHg, known to be associated to better outcomes over general anesthesia[24]. If not contraindicated (i.e., epilepsy), antifibrinolytics as tranexamic acid were administered in all the patients and hemostatic agents as fibrin sealant were used if bleeding was due to platelet deficiency or hepatic disease. Intraoperative blood recovery was applied if esteemed blood loss exceeded 10% of total blood volume. All patients underwent antibiotics prophylaxis with 2 g of intravenous cefazolin, 30 minutes before the start of the procedure; if any allergy to beta-lactam antibiotics was reported, 600 mg of intravenous clindamycin was administrated. Each patient was monitored for 120 minutes in the recovery room after the procedure, then moved to the ward and mobilized by the nurses 4 hours after the procedure.

All the patients underwent postoperative thromboprophylaxis with 10 mg of rivaroxaban, starting 8 hours after the operation and continued for 30 days; if not indicated, low-molecular weight heparin was administered. All the patients underwent standardized analgesic therapy for the surgery.

Omeprazole was administered to each patient for the 10 days following the surgery.

Post-operative Period

Postoperative blood loss reduction

Normothermia was maintained in all the patients. Proton pump inhibitors were administered to carry out a stress ulcers prophylaxis.

Postoperative optimization of physiological reserves for anemia tolerance

Hypothermia was avoided, precocious mobilization was allowed in all the fit patients, and high-risk patients were addressed to respiratory physiotherapy.

A restrictive blood transfusion approach was followed via constant monitoring of signs and symptoms of the single patient. Hemoglobin level cut-off for RBC transfusion was below 8 g/dL, according to a restrictive policy.

Our hospital provides, as standard of care, the admission to physical rehabilitation medicine (PRM) department after the first four postoperative days spent in the orthopedic ward. However, only stable patients were suitable for the transfer, therefore neither postoperative complications nor postoperative anemia should be present at the fourth postoperative day.

Statistical Analysis

We collected baseline characteristics including age, gender, type of surgery, Hb, ferritin, requested and transfused RBC bags, number of days spent in OR ward and in PRM ward.

The Chi-square or Fisher test were applied to analyze categorical variables, while the Student's *t*-test, Log-Rank, and Mann-Whitney were used for continuous variables.

ONE WAY ANOVA test was performed for each type of surgery, considering mean levels differentiated per year. A 95% confidence interval was used. A p-value of 0.05 or lower was considered statistically significant. p-values were corrected with Bonferroni method.

Results

A total number of 9,635 surgical patients who underwent a primary unilateral or bilateral TKA (2,314) or THA (7,321) between 2014 and 2019 were enrolled in our study. Median age of the surgical court was 63.6 years old. 45.6% are males and mean body mass index (BMI) is 28.61.

Total number of surgeries increased from 960 in 2014 to 1,421 in 2019 for THA, and from 219 in 2014 to 468 in 2019 for TKA (Figure 1).

Baseline patient characteristics, including hemoglobin ad ferritin concentrations were investigated 30 days prior to surgery. Patients who received ferric carboxymaltose (FCM) monotherapy on the day of preoperative assessment were 0% for all the surgeries in 2014. However, in 2019 were 18% and 19% (for unilateral and bilateral THA, respectively), and 20% and 23% (for unilateral and bilateral TKA, respectively). Mean hemoglobin level prior the surgery was analyzed over the years. In 2015, mean Hb levels were 14.4 g/dl and 14.5 g/dL for THA (unilateral and bilateral, respectively) and 13.6 g/dl and 14 g/dl for TKA (unilateral and bilateral, respectively). In 2019, mean Hb level was 14.2 g/dl and 14.5 g/dl for THA (unilateral and bilateral, respectively), and 14 g/dl and 14.7 g/dl for TKA (unilateral and bilateral, respectively).

No difference in anemia correction rates was observed in bilateral surgeries, but it should be noted that higher Hb concentration in this group was an admission criterion to the surgery itself and has been unchanged over the years. At the fourth postoperative day the Hb level was collected. In 2014, mean Hb levels were 10 g/dl and 9.1 g/dl for THA (unilateral and bilateral, respectively), and 10.3 g/dl and 10.2 g/dl for TKA (unilateral and bilateral, respectively). In 2019, mean Hb level at the fourth postoperative day was 10.7 g/dl and 9.9 Hb g/dl for THA (unilateral and bilateral, respectively), and 11.3 g/dl and 11.6 g/dl for TKA (unilateral and bilateral, respectively) (Figure 2). A statistically significant increase over the years in Hb level was observed for TKA (p=0.001).

As we can see in the Figure 3, the total number of requested RBC transfusion by each surgery over time has decreased, for THA (277 in 2014 *vs.* 120 in 2019, p=0.001). In parallel, the total number of performed RBC transfusions has decreased, for THA (167 in 2014 *vs.* 78 in 2019) (Figure 4).

No statistically significant differences were observed in the mean length of stay (LOS) in the OR ward through the years by each surgery, but an important decrease was observed in the total number of admitted patients to our PRM department (1,163 in 2014 *vs.* 471 in 2019; Figure 5), with a consequent significant reduction in the total days of hospitalization.

Afterwards, a more detailed analysis was performed to assess the correlation matrix between minimum level of Hb, BMI, age, days spent in OR ward and number of requested transfusions. As we can deduct from Figure 6, pairwise correlations are quite low, apart from transfusions and days spent in orthopedic ward, which shows a Pearson's coefficient greater than 0.5. This result testifies how the RBC bags transfusions were related to a lengthen in hospital stay in our surgical cohort.

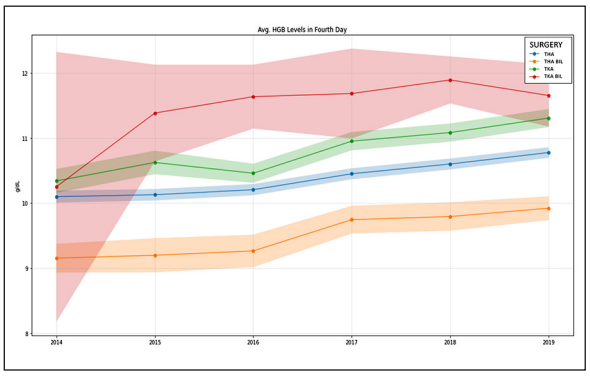

Figure 2. Variation over the years of mean Hb level at the fourth postoperative day.

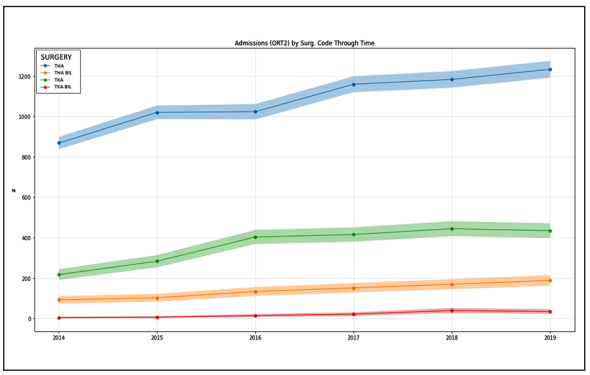

Figure 1. Orthopedic ward admission rate over time.

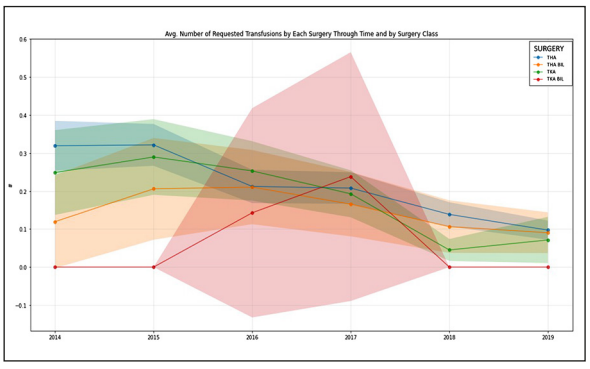

Figure 3. Number of requested transfusions by each surgery over time and by surgery class.

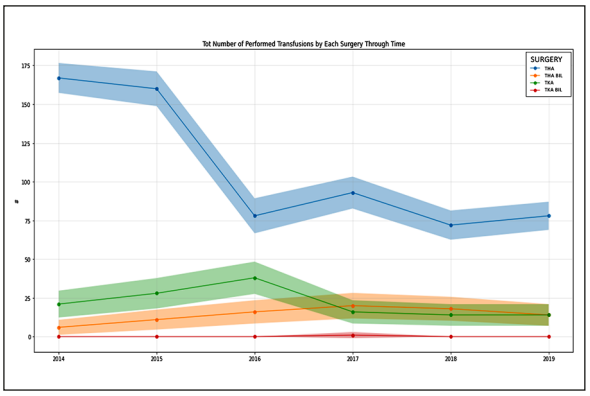

Figure 4. Number of performed transfusion by each surgery over time.

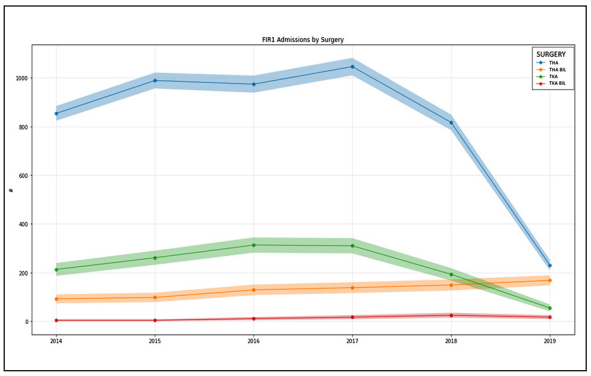

Figure 5. Physical rehabilitation medicine ward admission rate over time.

Discussion

In the last decade, the current conception of a PBM protocol, defined as "the timely application of evidence-informed medical and surgical concept designed to maintain hemoglobin concentration, optimize hemostasis and minimize blood loss in an effort to improve patients' outcome" has been progressively assimilated worldwide[25-27]. Nevertheless, to our knowledge, this is the first report on the comprehensive application of a PBM protocol in a large cohort of orthopedic patients in Italy.

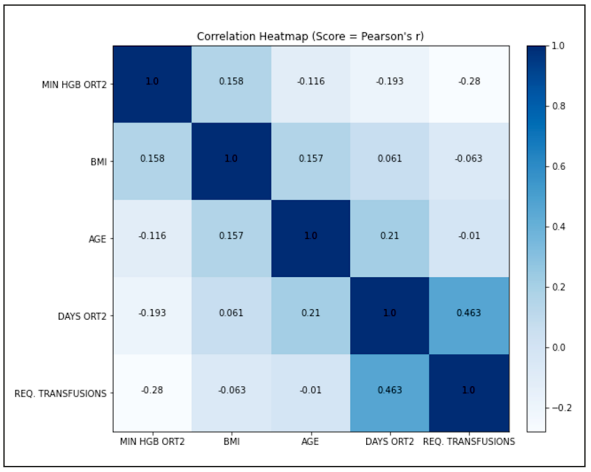

Figure 6. Correlation Heatmap (Minimum Hb level, BMI, age, days spent in orthopedic ward).

The most relevant PBM national protocol was first drafted in 2015 by the National Blood Center and introduced the use of iron supplementation to treat iron deficiency. In the past years, blood donations shortage represented an emergency mainly during holiday periods, due the decreased number of donators. Nowadays, the world pandemic exacerbated the chronic need of blood and even causes the suspension of elective surgery and the lengthening of the waiting list, therefore affecting the global patients' care.

Blood deficiency is currently much more difficult to manage also considering the ageing of population. The aforementioned reasons justify the need to preserve this resource by virtuous application of PBM protocols. However, consolidate working flow habits do not always allow a timely application of protocols containing just mere suggestions and recommendations. The introduction of a protocol must not interfere with the work of the personnel involved, and it must be accepted by the patients, with a further focus on economic sustainability.

A profound knowledge of the PBM protocol needs to be pursued even if hardly applicable in the current standard of care which still considers the blood transfusion the easiest and effortless therapeutical approach. We believe our data could represent a starting point to promote blood sparing approaches, therefore reserving transfusions only to selected patients, creating an optimization of resources available. Our work evaluated how the systematic application of a PMB protocol before and after surgery in a national referral center hospital, was able to influence patients' outcome in terms of RBC transfusions, reduced number of blood bags requested and early discharge from orthopedic ward[28,29].

The actual application in everyday practice of a PBM protocol encountered several difficulties: first, patient screening, then pre-operative treatment and discharge, particularly for patients coming from remote areas of Italy.

The PBM protocol consisted in a prompt application of the three pillars in the different peri-operative phases[25]. Our primary focus was the implementation of the pre-operative erythropoiesis

optimization[30]. Actually, a cumulative number of studies[31,32] validated the role of hemoglobin level in the patients' post-operative recovery. Morbidity and mortality of anemic patients is clearly higher when compared to patients with normal hemoglobin level[33,34]. These features appear fundamental in arthroplasty surgery where infections and complications are the major responsible for the outcome, for both stakeholders and the National Health System[9,35].

Our cohort revealed, among the predictive factors, how hemoglobin and ferritin levels assume a key role for both anemic and non-anemic patients.

For non-anemic patients, 'iron deficiency' was considered a ferritin level below the threshold of 100 μg/L; in this case, it is unlikely that, if undergone a major surgery with up to 10% of total blood loss, the patients will have prompt recovery without the need of blood transfusions. Moreover, previous studies[36-38] have shown that patients with low ferritin level undergoing surgery with an esteemed blood loss of at least 2 Hb points are unable to compensate such blood shrinkage.

To identify sideropenic patients, our preoperatory protocol was focused on early screening of hematopoietic asset, and a tailored approach during the 30 days prior to the surgery was adopted[13,36,39]. We considered an optimal hemoglobin level of 13 g/dL for both men and women, as suggested by PBM guidelines for elective surgery[22].

Additionally, these values were critically revised for each patient considering comorbidities, type of surgery, and blood loss estimate[19,40]. Indeed, for bilateral THA, an approximated hemoglobin loss of 2.9 g/dl per side was calculated, so only patients with a minimum level of 14 g/dl were considered suitable for surgery[3].

In order to assess the clinical efficacy of pre-operative treatment, the total number of transfusions and hemoglobin level at fourth day were examined. Our results demonstrated how the preoperatory Hb level optimization is associated to a higher level of Hb at the fourth post-operative day and it is inversely related to the total number of transfusions needed. Interestingly, from 2014, year of introduction of 'iron deficiency' diagnosis in our protocol, the mean level of Hb progressively increased during the years both at the fourth postoperative day and during the total hospital stay. Accordingly, iron storage implementation associated with blood loss containment and other strategies applied since 2014, contributed to a faster recovery of patients. From 2016, full PBM protocol application and a fast-track approach allowed early discharge from the orthopedic ward with no need to move the patient to the Rehabilitation Department.

The continuous clinical application of a PBM protocol in a high-volume hospital consisted of several phases. Firstly, personnel formation was fundamental to achieve the proper motivation among all the hospital staff involved; reasons behind the implementation of the PBM protocol, including the understanding of anemia tolerance and the importance of blood sparing for the patients were heavily stressed out[41-43]. Involvement of the general management of the hospital was fundamental to obtain the required resources as well. Lastly, patients' involvement was crucial from pre-admission to discharge. Moreover, the Ministry of Health, together with scientific societies, contributed on a nation-wide basis defining in 2015 the latest guidelines to optimize blood usage in the current clinical practice[26,44].

The use of tranexamic acid, intraoperative blood salvage, tissue-sparing surgery, balanced anesthesia, controlled blood pressure and warming of the patients were all fundamental measures to achieve the goal. We considered the PBM protocol funded on these three major pillars:

1. the patients' screening based on hemocrome, ferritin levels and C-reactive protein to identify patients at higher risk for post-operative transfusions;
2. the use of a specific iron supplementation, which could restore the iron shortage within a single administration;
3. the implementation of a PBM culture among all the medical team.

Limitations

The present study suffers from some limitations as well: firstly, its retrospective design and, secondly, the absence of a control group, which does not allow to establish whether the results obtained are directly attributable to the PBM application. Furthermore, the lack of hemocrome data of patients after their discharge prevented us from identifying any further effect of the PBM protocol in the middle-long term evaluation.

Nevertheless, our experience has shown how a timely application of a PBM protocol in the perioperative period can be significantly associated to reduction of blood transfusions and improvement of the clinical care, therefore offering clear benefits for both the patients and the hospital.

Conclusions

A comprehensive PBM protocol application in a national major orthopedic referral center was able to produce a significant increase in Hb level during the hospital stay in patients undergoing primary joint replacement and contributed to reduce the requests for blood transfusions thus leading to early discharge from the hospital.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

No funding to declare.

Ethics Approval

The Internal Review Board of IRCCS Humanitas Research Center approved the present retrospective study (ID No. 2315).

Authors' Contribution

M. Scardino wrote the draft of the paper; A. De Angelis, F. Martorelli, V. Simili, G. Monteleone, M. Bovio, F. Tasso, G. Grappiolo were responsible for the application of the PBM protocol and collection of data; G. Anzillotti, E. Kon, B. Di Matteo critically revised the paper; M. E. Laino, T. Tommasini, V. Savevski conducted the statistical analysis, T. D'Amato coordinated the writing and critically revised the last version of the paper. All the authors gave their approval to the final version of the present manuscript.

Informed Consent

All the patients gave their consent for the use of clinical data for scientific purposes.

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