

Volume 9 / Number 5 / 2015

ISSN 1840-2291

# HealthMED

Journal of Society for development in new net environment in B&H





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Published by DRUNPP, Sarajevo

Volume 9 Number 5, 2015

ISSN 1840-2291 e-ISSN 1986-8103

### HealthMED journal is indexed in:

- EBSCO Academic Search Complete
- EBSCO Academic Search Premier,
- EMBASE,
- SJR Scopus,
- Index Copernicus,
- Universal Impact Factor: Impact Factor is 1.0312 (UIF 2012)
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# The clinical manifestation of Robertsonian translocation

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## Abstract

Chromosomal abnormalities arise from change in number or structure of chromosomes. The most common interchromosomal rearrangements is Robertsonian translocation (centric-fusion translocations). Balanced Robertsonian translocation carriers are healthy and have a normal lifespan, but there is reproductive risks due to unbalanced segregation of the translocation or uniparental disomy. Unbalanced Robertsonian translocation, inherited or as de novo mutation, can lead to Down or Patau syndrome.

The aim of this study is to evaluate the clinical manifestation of detected Robertsonian translocation in patients who assessed cytogenetic analyse because of Syndrome Down, recurrent abortion history, and suspected Syndroma Turner.

The most common form of Robertsonian translocation was fusion between 14 and 21 chromosomes (40.74% cases), followed by fusion between 13 and 14 chromosomes (29.63% cases). Distribution of cytogenetic findings is statistical significant ( $p < 0.05$ ). Although Robertsonian translocation is the most common interchromosome rearrangement in humans, there are insufficient data about its clinical manifestation.

**Key words:** clinical findings, chromosomal aberration, balanced karyotype

## Introduction

Chromosomal aberrations reflects changes in portion of chromosomal DNA. Most chromosome abnormalities occur as an accident in parents or ancestors gametogenesis. Abnormalities associated with gain or loss of chromosome material cause specific genetic conditions. Structural rearrangements with no net change in chromosome material (balanced rearrangements) do not cause disease in carriers although they may lead to a reproductive problems.(1)

The most common interchromosome rearrangement is Robertsonian translocation (RT) with an incidence of 1.23 per thousand live births.(2) No environmental, dietary or lifestyle factors are known to cause RT. Chromosomes that possess an acrocentric centromere undergo such translocations. Those are from group D including 13, 14, 15 and group G including 21 and 22 chromosomes. During RT the participating chromosomes break at their centromeres and the long arms fuse to form a single chromosome. This fusion takes place in centromere area (centric-fusion translocation). The short arms which typically contains nonessential genes are lost. Isochromosome is formed by homologue chromosomes fusion.

In a case of trisomy developing embryo can 'correct' a trisomy by disposing of the spare third copy of the chromosome. This can leave two copies of the chromosome from the same parent - uniparental disomy (UPD). Chromosome 13, 21 or 22 are unlikely to be involved in UPD. Maternal UPD14 or Temple Syndrome, is characterized by low birth weight, hypotonia, early puberty and markedly short adult stature.(3) Typical features of paternal UPD14 or Kagami-Ogata syndrome include polyhydramnios, thoracic and abdominal wall defects, growth retardation and severe developmental delay.(4) Paternal UPD15, Angelman syndrome is characterized by neurodevelopmental disorders: ataxic movements, developmental delay, intellectual disability, and epilepsy.(5) Maternal UPD15, Prader-Willi syndrome is characterized by prenatal and/or postnatal growth retardation, mental retardation, neonatal hypotonia, hypogenitalism, hypopigmentation, obesity/hyperphagia.(6)

Balanced RT between heterologous chromosomes do not affect lifespan, and can be passed down in families for many generations. Adult RT carriers with normal phenotype can have fertility problem associated with more or less severe oligospermia in males and miscarriage or infertility

in females.(7) However, phenotype of balanced RT karyotype in children are very rare described. Phenotypes associated with balanced RT that include t(13; 14)(q10; q10) range from growth hormone deficiency to precocious puberty.(8) Autosomal genes can have possible role in the pathogenesis of ovarian follicular attrition how karyotype with balanced RT [45, XX, rob(15; 21)] was associated with premature ovarian failure.(9)

Balanced RT bears risk of trisomy 21 (Down Syndrome) and trisomy 13 (Patau Syndrome).

Unbalanced RT can be de novo mutation or inherited from parents.

The aim of this study is to evaluate the clinical manifestation of detected RT in patients who assessed cytogenetic analyses during twenty years period (1985-2004) in "Center for human genetics" of Medical faculty in Sarajevo.

### Materials and methods

This study is retrospective evaluation of RTs findings during cytogenetic examinations of the population from the Federation of Bosnia and Herzegovina during twenty years period (1985-2004) which were done in „Centre for human genetics" of Medical faculty in Sarajevo.

Chromosomal analyses were performed on chromosomes prepared from cultivated peripheral lymphocytes. For precise identification of chromosomes standard method for G-banding was used.(10) Twenty-five metaphases were analyzed.

### Results

In the retrospective study for a twenty years period (1985-2004) cytogenetic investigation was done in 27 patients having Robertsonian translocations who were sent for cytogenetic analysis because of Syndrome Down (15 cases), recurrent abortion history (11 cases), and suspected Syndrome Turner (1 case). Karyotypes with different forms of RT are listed in table 1.

Among all examined cases, the most frequent (40.74%) cases were with RT formed by fusion between heterologous chromosomes 14q and 21q, followed by fusion between heterologous chromosomes 13q and 14q (29.63%) and fusion between heterologous chromosomes 13q and 21q (14.81%). RT composed of homologous chromosomes 21q; 21q was demonstrated in 14.82% of cases. None of RTs involved 15 and 22 chromosomes. Distribution of cytogenetic findings is statistical significant ( $p < 0.05$ ).

Table 1. Detected forms of Robertsonian translocation

Gender	Karyotype with RT	Clinical findings	Number of detected cases		All	
			N <sup>0</sup>	%	N <sup>0</sup>	%
mail female	46,XY,rob(21; 21)(q10; q10) 46,XX,rob(21; 21)(q10; q10)	Syndrome Down	3 1	75.00 25.00	4	14.82
mail female	46,XY,rob(14; 21)(q10; q10) 46,XX, rob(14; 21)(q10; q10)	Syndrome Down	2 6	25.00 75.00	8	29.63
female	45,XX, rob(13; 21)(q10; q10)	Child with Syndrome Down	1	100.0	1	3.70
mail female	46,XY, rob(13; 21)(q10; q10) 46,XX, rob(13; 21)(q10; q10) 46,XX, t(4; 14)(q27; q33), rob(13; 21)(q10; q10)	Syndrome Down	1 2	33.33 66.67	3	11.11
mail female	45,XY, rob(14; 21)(q10; q10) 45,XX, rob(14; 21)(q10; q10)	Child with Syndrome Down	2 1	66.67 33.33	3	11.11
mail female	45,XY, rob(13; 14)(q10; q10) 45,XX, rob(13; 14)(q10; q10)	History of recurrent abortion Offspring with reproductive problem (proband mother) Suspected Syndroma Turner	4 4	50.0 50.0	8	29.63
Total					27	100.00

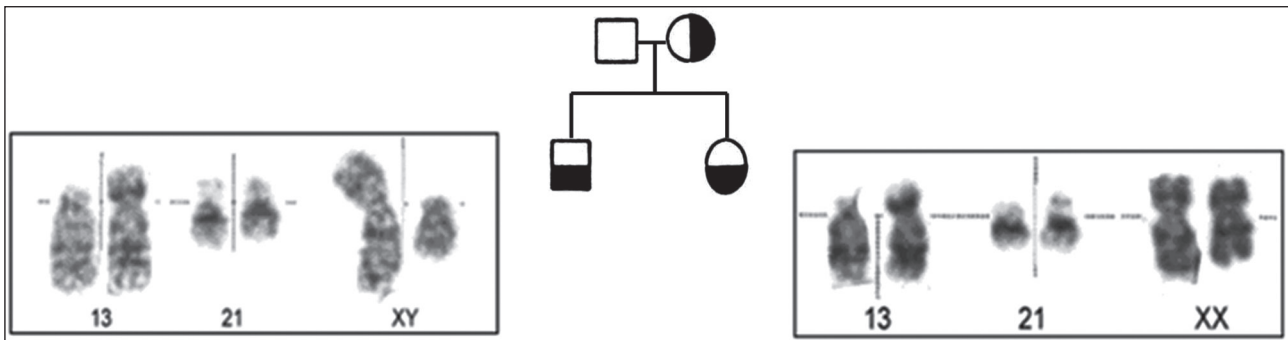


Figure 1. Pedigree with a 13; 21 Robertsonian translocation. Symbols:  $\square$  = normal male karyotype;  $\circ$  = balanced  $t(13; 21)$ ;  $\blacksquare$  = trisomy 21, unbalanced  $t(13; 21)$

Balanced RT is demonstrated at 12 (44.44%) examiners. Eight cases involved rob(13; 14), three involved rob(14; 21), and one involved rob(13; 21). Unbalanced RT is demonstrated at 15 (55.56%) examiners. All cases of unbalanced RT were associated with Syndrome Down. Four of them were due to rob(21; 21) (q10; q10), eight due to rob(14; 21) (q10; q10) and three due to rob(13; 21) (q10; q10). All cases with rob(21; 21) (q10; q10) were de novo mutation.

Familiar transmissions were uncovered in proband and her mother, carriers of balanced RT with rob(13; 14) (q10; q10), and in five cases of unbalanced RT. Three of these unbalanced RT included rob(14; 21) (q10; q10) and two included rob(13; 21) (q10; q10). Rob(13; 21) (q10; q10) was presented in brother and sister who underwent the cytogenetic analysis because of Syndrome Down. Because of their cytogenetic results [46, XY, rob(13; 21) (q10; q10) and 46, XX, rob(13; 21) (q10; q10)] both parents were investigated. Father had normal karyotype: 46, XY, whereas mother had balanced RT between heterologous chromosomes 13q and 21q: 45, XX, rob(13; 21) (q10; q10) (Figure 1).

In one patient, who had cytogenetic analysis because of clinically diagnosed Down syndrome, karyotype was multiple changed: 46, XX,  $t(4; 14)$  (q27; q33), rob(13; 21) (q10; q10) (Figure 2). While RT between chromosomes 13 and 21 was de novo mutation, cytogenetic analysis of father uncovered the familial transmission of  $t(4; 14)$  (q27; q33) (Figure 3).



Figure 2. Karyotype of probande: 46, XX,  $t(4; 14)$  (q27; q33), rob(13; 21) (q10; q10)

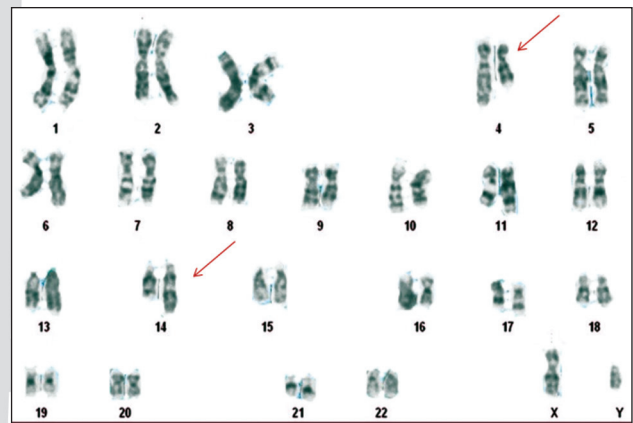


Figure 3. Balanced karyotype with translocations between 4 and 14 chromosomes: 46, XY,  $t(4; 14)$  (q27; q33)

## Discussion

In the retrospective study for a twenty years period (1985-2004) cytogenetic diagnosis was performed in 27 patients having RTs who were sent for cytogenetic evaluation because of Syndrome



Down and recurrent abortion history, as often manifestation of RTs. There was one case with suspected Syndrome Turner. Short stature, main clinical manifestation of Syndrome Turner, is often overlooked in practice. Choi et al. observed phenotypes in patients with RTs. The study included eight boys with 45, XY, t(13; 14) (q10; q10) and three girls with 45, XX, t(13; 14) (q10; q10) karyotypes whose phenotypes range from hypogonadotrophic hypogonadism, precocious puberty, to growth hormone deficiency, and short stature.(8)

In this study none of RT was uncovered due to UPD in offspring.

Among the 27 karyotypes with RT, the occurrence of rob(14; 21) in 40.74% cases is higher than rob(13; 14) found in 29.63% cases. This is not according the general population percentage frequency of these types of RT reported in the literature by which the majority (73 %) of RTs occurs between chromosomes 13 and 14, and 10 % of RTs involve chromosomes 14 and 21.(11) This can be explained by sample in which chromosomes aberrations apparently can be connected with clinical condition.

Balanced RT is demonstrated in 12 (44.44%) examiners. Eight cases involved rob(13; 14), three involved rob(14; 21), and one involved rob(13; 21). Carriers of rob (13; 14) carry increased reproductive risks due to unbalanced segregation of the translocation or uniparental disomy 14.(12) In present study none trisomy 13 or UND 14 was connected with rob(13; 14), although one familiar transmission was uncovered. Generally rob(13; 14) associated trisomy 13 is rare because there is high frequency of balanced gamete resulting from alternate segregation.(13) This translocation can be segregated through several generations with no clear-cut effect on fertility.(14) While the risk for unbalanced offspring is low in RTs between heterologous chromosomes that not include 21, there is high risk for trisomy in offspring if chromosome 21 is included in RT. In this study all balanced RTs involving chromosomes 21 were uncovered because carriers were assessed for cytogenetic evaluation after Syndrome Down was proved in offspring.

Unbalanced RT is demonstrated at 15 (55.56%) examiners. All cases of unbalanced RT were associated with Syndrome Down. Four of them were due to rob(21q; 21q), eight due to rob(14; 21) (q10;

q10) and three due to rob(13; 21) (q10; q10). For three cases included rob(14; 21), and two included rob(13; 21) familiar transmission was found. The rest was de novo mutation. In patient, who has cytogenetic analysis because of clinically diagnosed Down syndrome, karyotype was multiple changed: 46, XX, t(4; 14) (q27; q33), rob(13; 21) (q10; q10). While RT between chromosomes 13 and 21 was de novo mutation, cytogenetic analysis of father uncovered the familial transmission of t(4; 14)(q27; q33). Although no environmental, dietary or lifestyle factors are known to cause RT, chromosome balanced rearrangements during gametogenesis may show asynaptic regions that may interfere with the pairing and segregation of other unpaired segments of the remaining chromosomes (phenomenon termed interchromosomal effect). This may result in accumulation of numerical and structural chromosome imbalances in spermatozoa and add aneuploidy for the chromosomes not involved in the rearrangement. (15) Fifty-four percent of men with Robertsonian translocations, 44% of reciprocal translocation carriers and 7% of men with inversions have been reported to carry an added aneuploidy load in the form of an interchromosomal effect in the sperm. (16)

## Conclusion

Although Robertsonian translocation is the most common chromosome rearrangement in humans, there are insufficient data about its clinical manifestation.

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# Surgery scheduling: Implementing a priority score for elective surgeries

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## Abstract

**Introduction:** Surgical map construction is a complex activity, especially in hospitals that perform various specialized operations. Most work that addresses this topic has focused on resource optimization and better operating room time occupation. We did not find any articles in which clinical criteria were used to prioritize scheduling.

**Objective:** To present an instrument created at Cariri Regional Hospital to prioritize elderly patients and patients with comorbidities.

**Method:** This descriptive study aims to propose a “priority score” instrument for optimizing surgery scheduling in hospitals with a high level of complexity. This study was conducted in the city of Juazeiro do Norte, Ceará, Brazil, in a highly complex hospital setting with eight operating rooms and demands for various specialties.

**Result:** We observed a reduced elective surgery cancellation rate, facilitation in conducting operating room movement, and fewer conflicts within the institution.

**Conclusion:** Implementation of the priority score facilitated the development of a surgical map, thus providing more dynamic service, shorter periods of operating room idleness, and better uses of available human materials at every turn; accordingly this allows the exchange of information between professionals from different sectors of the hospital.

**Key words:** surgical map; scheduling; priority; suspension; score

## Introduction

The creation of a surgical map is a complex activity, particularly in the context of large hospitals

with many surgical specialties.<sup>1</sup> At most institutions, this procedure does not receive the necessary attention and the person responsible for scheduling often has no background in health.

Schedulers are mid-level professionals who often find themselves in delicate situations in which they must decide between two or three surgeries while under pressure from surgeons and resident physicians. The resulting models generate conflict and dissatisfaction among patients and professionals and have negative impacts on surgery cancellation rates and service quality.<sup>2</sup>

Most work related to surgery scheduling aims to reduce costs and optimize the operating room usage time in order to avoid delays and surgery cancellations.<sup>3</sup> Much of this work involves complex equations that are not practical for daily usage.

Accordingly, as inefficient scheduling may lead to additional patient harm and grievances and a lack of optimization with respect to surgeons' work processes, we believe that it is important to generate a simple tool that will convert surgical map into a practical process through the use of forms filled out by anaesthesiologists in agreement with other healthcare professionals.

The aim of this study was to present a surgical scheduling prioritization tool based on a form containing well-defined criteria in order to create a score according to which each patient can be classified using objective numerical values based on their clinical condition.

Studies that propose tools intended to facilitate surgical map creation using objective priority criteria while considering the human resource availability per shift and the operating room availability of the surgical centre may reduce the elective sur-

gery cancellation rates and simplify the scheduling process.

## Methods

This descriptive study proposed the “priority score”, a tool intended to optimize surgery scheduling in hospitals with a high level of complexity.

This study was performed in a hospital with a high level of complexity in the municipality of Juazeiro do Norte, Ceará, Brazil. This hospital includes eight operating rooms and is in demand for several specialties.

After evaluating the surgery scheduling process at this hospital, the need for reorganization intended to optimize patient selection according to their needs became clear; accordingly, the “priority score” was created to facilitate the scheduling process.

The priority score generates a value for each patient; values range from 2 to 13, with 13 indicating the highest priority and 2, the lowest priority. This scoring system includes elderly patients, patients with diabetes, higher physical condition, those with a higher surgical risk, those from the intensive care unit (ICU) or infirmary ward, those with fractures, those undergoing vascular surgery, and those for whom previous procedures were previously suspended for some reason (Table 1).

The score table was added to the pre-anaesthetic evaluation sheet; the anaesthesiologist was res-

ponsible for completing the table and inserting the total priority value in the surgery notice. The notice was then forwarded to the Customer Support Centre (CSC) for scheduling, and higher scores were prioritized (Figure 1).

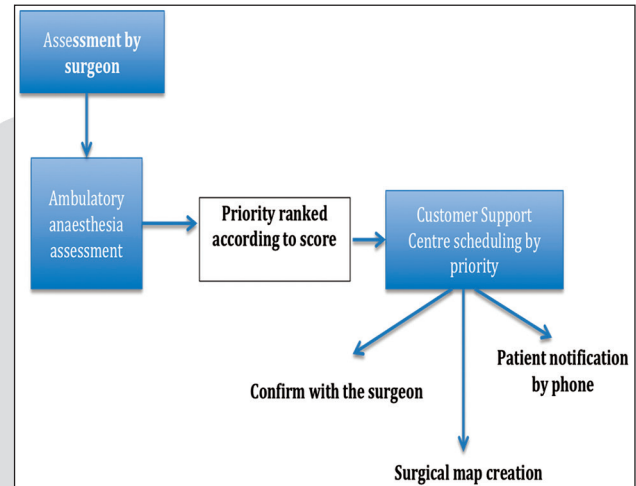


Figure 1. Ambulatory flow prior to creation of the surgical map

## Results

The priority score was implemented in October 2014 with the objective to facilitate the scheduling process and, consequently, have a positive impact on surgery cancellation rates and optimize the operating room usage time; this latter metric decreased by 50% during the month following score implementation (Figure 3).

Table 1. Priority scores used to create the surgical map

Priority score					Total
Age	>75 Years 1	<75 Years 0			
Diabetes	No 0	Yes 1			
Physical condition	ASA I 1	ASA II 2	ASA III 3	ASA IV 4	
Surgery risk	Low Risk 1	Moderate Risk 2	High Risk 3		
Origin	Home 0	Infirmary 1	ICU 2		
Previously cancelled procedure	No 0	Yes 1			
Fractures or vascular surgery	No 0	Yes 1			
Total					

ASA, American Society of Anaesthesiologists; ICU, intensive care unit

Table 2. Surgical durations according to surgeon and surgery type, evaluated between September and November 2014

Surgeon	Cholecystectomy duration	Inguinal hernioplasty duration	Femoral fracture duration	Tibial fracture duration
Surgeon A	70 (45–85) min	55 (47–64) min		
Surgeon B	62 (50–74) min	70 (61–75) min		
Surgeon C	65 (55–72) min	57 (52–63) min		
Surgeon D	72 (61–81) min	68 (64–73) min		
Surgeon E	56 (52–63) min	54 (50–59) min		
Surgeon F			90 (82–98) min	45 (35–50) min
Surgeon G			95 (85–102) min	49 (44–54) min
Surgeon H			85 (81–92) min	52 (48–56) min
Surgeon I			70 (65–90) min	48 (43–54) min
Surgeon J			87 (81–95) min	60 (55–64) min

Surgeons' and anaesthesiologists' shift schedules became based on surgical schedules to avoid idleness and conflicts resulting from poor team design as well as situations in which shifts involving five surgical specialties were required to have five assigned anaesthetists. In addition, a 30-minute tolerance period at the beginning of surgery was implemented into the scheduled surgical time to avoid surgery cancellations.

This criteria-based scheduling process revealed the need to know the average time for each surgery and surgeon in order to optimize functioning of this service (Table 2). Therefore, surgeries were scheduled according to priority, using the average time for the proposed surgery as well as the cleaning and preparation times listed for the operating room and the assigned medical team (Figure 2).

## Discussion

Several studies focused on surgery scheduling have been conducted worldwide, most with the aim of maximizing the operating room usage time efficiency, have been published in the literature.<sup>4-10</sup>

Some of those studies used complex equations to calculate the average surgery durations for each

surgeon and used these values in addition to their respective standard deviations to create surgical maps (Table 2). Other studies used computerized models to simulate several scheduling strategies. The present study offers a new patient-focused perspective while emphasizing the cost benefits to the scheduling service and using predicted surgery times provided by the surgery team.<sup>9-12</sup>

The lack of well-defined criteria for managing demands at a surgery centre may lead to high cancellation rates and frequent conflicts between surgeons, as each attempts to treat their patients according to their own personal schedules and interests. These events result in delays, disturbances, and reductions in patient safety, which should be the main aim of this assistance.<sup>13</sup>

Figure 2 shows the surgical scheduling model used in the hospital in which this study was performed. This schedule was shared on a Google Drive and was therefore available to all surgeons and anaesthesiologists, who could view their surgery schedules at any time.

In this service, surgeons and coordinating anaesthesiologists at the Surgical Centre were frequently consulted and questioned, leading to eventual conflicts. There were no interactions between pro-

Thursday 15/10/2014	Anaesthesiologist	7:30	8:30	9:30	10:30	11:30
	Anaesthesiologist A	Emergency		Emergency		
	Anaesthesiologist B	COLONOSCOPY p. 10287 Score 5 Surgeon E		COLONOSCOPY P. 99232 Score 2 Surgeon E		
	Anaesthesiologist C	CALCANEUS FRACTURE P. 104191 Score 7 Surgeon A		TIBIAL PLATEAU FRACTURE P. 17275 Score 3 Surgeon A		
	Anaesthesiologist D	CHOLECYSTECTOMY VDL P. 104615 Score 5 Surgeon C		OSTEOSYNTHESIS OF A ZYGOMATIC FRACTURE P. Score 2 103449 Surgeon D		

Figure 2. Scheduling model created using the priority score



professionals, and meetings were required at the end of each day in an attempt to organize the surgical map.

After implementing the priority score based on objective criteria, a mid-level professional began to schedule surgeries, which resulted in an impact on the nearly 25% surgery suspension rate. This rate subsequently decreased to 5.7%, although it is not known whether this was coincidental (Figure 3).

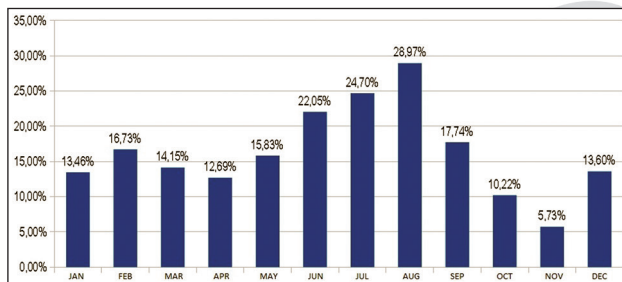


Figure 3. Surgery cancellation rates by month during the year 2014

It is likely that patient-focused surgical scheduling will yield similar results to those achieved using algorithm- and statistical formula-based scheduling. Some consulted studies used *Student's t* and *Pearson* distributions to generate complex equations that cannot be used practically on a daily basis.<sup>13-15</sup>

The proposed priority score was proven to be practical, functional, and easily applied, and it allowed surgical map scheduling in accordance with patients co-morbid conditions, thus enabling such patients to undergo surgery earlier in the day and with shorter waiting times between the release from ambulatory anaesthesia and completion of the proposed procedure.

Another positive aspect of priority criteria implementation was the mandatory execution of a pre-anaesthetic evaluation for all patients.<sup>9</sup> The priority score became mandatory for the surgery scheduling.

Priority score implementation also required the registration of each surgeon's and procedure's surgery times, thus allowing the optimization of operating room time usage.<sup>8</sup> In a second step, it became clear that the operating room cleaning and preparation times must also be registered. These measures facilitated the fulfilment of the surgery program and the suggested schedules on the map.

Another positive aspect of priority score implementation was the interactions between different medical specialties, resulting in a better distributi-

on of work assignments. Three elective surgeries were scheduled for each shift with four anaesthetists, thus providing one available anaesthesiologist for the emergency services and prioritizing patients based on the previously listed criteria.<sup>15</sup>

The predicted surgery durations and requirement of compliance with the procedural start times resulted in an increase in patient satisfaction and decreases in surgeons' wait times as well as patients' fasting durations.

In addition to simplifying surgical map creation, the priority score served as a quality filter for the pre-anaesthetic evaluations performed by both the ambulatory service and other services.

Patients from other services whose pre-anaesthetic evaluations had been performed at those services' ambulatory units were required to undergo priority score evaluation. If the priority score could not be concluded from the provided data, the data were considered incomplete based on the hospital's criteria and the patient underwent mandatory re-evaluation according to the hospital's standards before being directed to scheduling.

The implementation of this priority score, which incorporated clinical criteria associated with operating room availability, average durations of scheduled surgeries, and human resources, improved the dynamics of the service in terms of better operating room usage time management and contributed to a reduction in surgery cancellation rates.<sup>12</sup>

When creating a surgical map, it is necessary to use criteria based on the patient's clinical condition, logarithmical equations, or computerized models to prevent spontaneous demands from affecting the service's performance. As shown previously, the establishment of well-known criteria for surgery scheduling facilitates the logistics of the service and provides benefits that mainly affect the patient.<sup>15</sup>

## Conclusion

Surgical scheduling is a challenge for the coordinators and direction boards of hospitals that perform surgeries involving several specialties. It is up to these professionals to administer these services according to demand while considering the numbers of available operating rooms and professionals during each shift and the average procedural durations in addition to prioritizing patients

with poorer clinical conditions such that their procedures occur earlier in the day.

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# Neutrophil-lymphocyte ratio as disease activity indicator in *Multiple Sclerosis* patients

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## Abstract

**Introduction:** MS is an inflammatory disease. The neutrophil/lymphocyte ratio (NLR) was found to be a simple and low-cost inflammatory marker, which was investigated in diseases with inflammatory features during the acute phase, such as malignancies and acute coronary events.

**Objective:** The main objective of this study is to investigate whether NLR may be used as an acute marker of disease during the active stage in patients with MS.

**Material and Methods:** Participants were 88 MS patients in the exacerbation and/or remission period and 89 healthy individuals. The functional status of MS patients was evaluated using Expanded Disability Status Scale (EDSS). Mean NLR values of both control group and study group in the exacerbation and remission were evaluated. Data obtained was evaluated using, mean, standard deviation, one way ANOVA Test and Pearson Correlation Analysis.

**Results:** The mean NLR values of the MS patients were during attack and remission period  $4.71 \pm 3.62$  and  $2.25 \pm 1.07$  and of the control  $1.80 \pm 0.66$ . MS patients' mean NLR values were higher than compared to remission period and to controls ( $p < 0.001$ ). No statistical difference in the mean NLR values obtained during the remission period of the MS patients and the of the control group ( $p > 0.005$ ) and no correlation could be seen between the NLR values and EDSS, disease period, age, and BMI scores  $r: 0.153$ ,  $r: 0.009$ ,  $r: -0.015$ , and  $r: -0.017$  respectively.

**Conclusion:** Findings show that the mean NLR values of the MS patients in the exacerbation period were higher compared to the remission period and healthy controls indicating a relationship between disease activity and NLR.

**Key words:** Multiple sclerosis, Neutrophil, Lymphocyte, indicator

## Introduction

Multiple sclerosis (MS) is a neurodegenerative disease characterized by inflammation, demyelination, and glial sclerosis and the disease may involve many parts of the central nervous system. MS patients may have various and variable symptoms depending on the involved area of the central nervous system, often presenting with motor, somatosensory, visual, cognitive, and psychiatric disorders<sup>1</sup>. While the exact etiology of the disease is still unknown, it is considered to be multifactorial. However, it is definitely known to be an inflammatory disease resulting in demyelination<sup>2</sup>. In recent years, an index began to be used, which reflects both increased neutrophil count showing the acute condition in inflammation and lymphopenia that develops following acute physiological stress<sup>3</sup>. The neutrophil/lymphocyte ratio (NLR) was found to be a simple and low-cost inflammatory marker, which was investigated in diseases with inflammatory features during the acute phase, such as malignancies and acute coronary events<sup>4</sup>. This index obtained with NLR was used along with other inflammatory markers in studies and was found to be a good marker of inflammatory condition. The main objective of this study is to investigate whether NLR may be used as an acute marker of disease during the active stage in patients with MS.

## Materials and Methods

A total of 88 patients (58 females, 30 males), with a confirmed diagnosis of MS, and a total of 89 healthy subjects (the control group; 57 females, 32 males), matched for age and gender characteristics were included in the study at Konya Training and Research Hospital between 01.01.2012 and 01.01.2014. The Expanded Disability Status Scale (EDSS) values showing functional status, disease



durations, and medications used by the MS patients were retrospectively recorded. MS patients who had infections determined by laboratory examinations or other inflammatory diseases, chronic lung disease, chronic liver disease, or chronic infection in their records were excluded from the study.

The MS patients who were included in the study were divided into two groups and control subjects were included in Group 3.

- Group 1: The magnetic resonance images (MRI) of the patients were retrospectively analyzed. Neutrophil and lymphocyte counts of a total of 88 patients (58 females, 30 males) in their acute stages with active plaque of MS disease were collected from the complete blood counts performed during that stage and NLR values were calculated.
- Group 2: Neutrophil and lymphocyte values were retrospectively recorded from the complete blood count examinations of the same patients performed during the non-active remission stage and NLR values were calculated.
- Group 3: Neutrophil and lymphocyte values were retrospectively collected from the complete blood count examinations of 89 subjects included in the control group and their NLR values were calculated.

Age, height, and body-mass index (BMI) values of all three groups were retrospectively recorded.

The statistical evaluation was performed electronically using the SPSS software package version 21. Standard deviation, one-way ANOVA test, and Pearson's correlation analysis were used to evaluate the data of all three groups. The distribution normality was analyzed using the Kolmogorov-Smirnov test. The descriptive data were presented as mean  $\pm$  standard deviation. Independent double sampling t-test was used in the parametric distributions for the difference between the three groups, and the Kruskal-Wallis test was used for the difference between between-group non-parametric numerical values in multiple groups. The Mann-Whitney U-test was used for the Kruskal-Wallis post-hoc analyses. Pearson's chi-square ( $\chi^2$ ) test was used for the difference between variables. A value of  $P < 0.05$  was accepted as statistically significant.

## Results

There was no statistically significant difference between the patients and the control group with respect to age and BMI values, as shown in Table 1 ( $p > 0.005$ ).

When patients' NLR values during the attack stage were compared with their remission stage values and the NLRs of the controls, the mean NLR value of the patients during the attack stage were higher than the other two mean values and statistically significantly different ( $p < 0.001$ ). There was no difference between the NLR values of

Table 1. Demographic characteristics of patients and control group

	MS(N=88)	Control(N=89)	p value
Age	35.66 $\pm$ 10.07	36.29 $\pm$ 10.73	0.889
BMI	24.94 $\pm$ 2.97	25.93 $\pm$ 4.25	0.760
Disease duration	6.02 $\pm$ 4.80	-----	
EDSS	1.82 $\pm$ 1.61	-----	

EDSS: Expanded Disability Status Scale, BMI: Body Mass Index

Table 2. Mean neutrophil/lymphocyte ratios of all three groups

	Mean NLR values	p value
MS attack	4.71 $\pm$ 3.62	0.000*
MS remission	2.25 $\pm$ 1.07	0.000**
Control	1.80 $\pm$ 0.66	0.356***

P\* The statistical difference between MS-attack and MS remission,

P\*\* The statistical difference between MS-attack and control group,

P\*\*\* The statistical difference between MS-remission and control group,

NLR: Neutrophil/lymphocyte ratio

Table 3. The correlation between NLR and EDSS, disease duration, age, and BMI scores

	Neutrophil/Lymphocyte ratio	
	r (s)	p value
EDSS	0.153	0.156
Disease duration	0.009	0.930
AGE	-0.015	0.869
BMI	-0.017	0.878

NLO: Neutrophil/lymphocyte ratio, EDSS: Expanded Disability Status Scale, BMI: Body Mass Index

the patients in remission and the NLRs of the controls ( $p=0.004$ ).

No correlation was found between NLR and EDSS, disease duration, age, and BMI scores in patients in MS attack stage (Table 3).

### Discussion

MS is a chronic inflammatory, demyelinating disease of the central nervous system (CNS). MS begins during early adulthood. Despite important advances in treatment in recent years, it remains the leading cause of neurological disability in the white population<sup>5</sup>. While the etiology of MS is not fully known, many findings indicate that the immune system plays an important role in the disease pathogenesis. Moreover, genes and environmental factors also increase the risk of developing the disease. Family and genetic studies show that MS has a polygenetic mode of inheritance. The human leukocyte antigen (HLA) region is the only major gene locus associated with disease<sup>6</sup>. Migration studies, studies on MS epidemics, and the association between relapses and viral infections, support an additional role for environmental factors (particularly infections) in the pathogenesis of MS<sup>7</sup>.

CD4+ T cells are known to play a key role in the development of experimental allergic encephalomyelitis (EAE), which is considered as the experimental model for MS. In light of this finding, MS is thought to be a disease primarily driven by T cells. While there are many studies investigating the role of CD4+ T cells in MS, the role of these cells in the pathogenesis of MS has not been fully clarified<sup>8</sup>. CD4+ T cells specific to myelin proteins were found in the blood and cerebrospinal fluid (CSF) of MS patients. However, the presence of these cells also in healthy controls makes it more difficult to associate this disease directly with their

presence<sup>9</sup>. Inflammatory T cells are formed by active macrophages or microglial cells. This inflammatory process is associated with the destruction of BBB and local expression of pro-inflammatory cytokines and chemokines.

Inflammatory mediators may play a role in the axonal damage during the acute stage of the disease. Moreover, an association was found between CD8+ T cell count and the level of axonal damage and an axon damage mechanism at the level of MHC class I was also proposed<sup>10-11</sup>. Macrophages and microglial cells in close contact with axons may also cause axonal damage by releasing proteases, cytokines, and free radicals<sup>12</sup>. There are also findings that indicate that axonal damage may occur due to the effect of axon-specific antibodies<sup>13-14</sup>. It was also shown that low-level axonal degeneration continued to occur in silent, inactive plaques without marked inflammation<sup>15</sup>.

In this study, the researchers investigated whether NLR is a simple marker to facilitate the diagnosis of an attack by making a comparison with non-active stage of the disease and healthy controls. As a result of this study, the researchers believe that NLR can be used as a simple, non-invasive, and low-cost parameter in demonstrating acute inflammation during the acute stage of MS, and neutrophils are more active in the disease pathogenesis during the acute disease stage.

MS pathology is defined as the presence of primary demyelinating plaques in the brain and spinal cord and as an inflammatory process. Inflammatory T cells are formed by active macrophages or microglial cells. This inflammatory process is associated with the destruction of the blood-brain barrier and local expression of pro-inflammatory cytokines and chemokines. Demyelination is accompanied by acute axonal destruction and axonal loss at varying degrees<sup>16</sup>.

Currently, inflammation is considered to be a local reaction followed by the accumulation of fluid and blood cells in live tissues as a response to local damage. The inflammatory reaction may be acute or chronic, depending on the quantity, quality, and duration of the stimulus. An acute reaction is known as an accumulation of fluid and plasma proteins accompanying neutrophil recruitment, which may last from several minutes to several days. A chronic reaction, however, lasts longer, possibly days or months, and is characterized by the presence of lymphocytes and macrophages in the inflamed tissue, proliferation of blood vessels (angiogenesis), and connective tissue proliferation (i.e. fibrosis)<sup>17-19</sup>.

Although the effect of inflammation was initially defined as detrimental, as the immunological character of inflammation, contributing cells, and outcomes were more clearly defined, it was understood that it does not only have detrimental effects, but also may have beneficial effects. MS has a heterogeneous immunopathogenesis<sup>20</sup> and the location and importance of inflammation in the process are also different in different pathological subgroups. When MS plaques with active demyelinating are examined, it is seen that MS patients have both structural and immunopathogenic differences in inflammation, demyelination, and oligodendrocyte pathology<sup>21</sup>.

Recent studies have shown that neutrophil/lymphocyte ratio (NLR) is a strong indicator in determining inflammation in cardiac and non-cardiac diseases. Tokgöz et al. advocated that NLR could be a marker of early mortality in acute stroke with a predominance of inflammation<sup>22</sup>. Özler et al. reported that NLR was an inflammatory marker and a prognostic factor in facial paralysis<sup>23</sup>. Öztürk et al. found a moderate degree of correlation with CRP and NLR as inflammation markers in Behcet's disease<sup>24</sup>. Tanindi et al. defined NLR as an easily accessible inflammatory marker in coronary artery disease caused by an inflammatory process, such as atherosclerosis, and advocated that it could be used to determine disease prognosis<sup>25</sup>.

Parallel to the above mentioned studies, the results of the current study demonstrated that inflammation is predominant during the acute stage of MS and that NLR was high, indicating the effectiveness of neutrophils in the development mechanism of inflammation during the acute stage.

Since the researchers could not find any study on NLR ratio in acute-stage MS patients, additional and advanced studies are needed to establish NLR as a parameter that is an early marker of the attack stage of the disease, to determine a cut-off value indicating the attack stage in MS, and to determine whether NLR has a role in prognosis.

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# Good medical leadership assessed by doctors in training

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## Abstract

**Introduction:** Medical leadership has only recently begun to be part of common medical terminology. Medical leadership consists of fully trained physicians occupying management positions relevant to practice of medicine. The need to further develop leadership skills of physicians has opened up a discussion to increase leadership studies also in medical training.

**Methods:** Essays on good medical leadership and doctors as leaders in healthcare organizations. The essays (n=225) were written as part of leadership and management training for specialist degree in medicine in a Finnish university during years 2012-2013.

**Results:** As assessed by specializing physicians, good medical leadership of doctor leaders consists of interpersonal and communication skills, appropriate management of medical expertise, and people and resources management abilities. In the results, emphasis was put on interpersonal and clinical skills of doctor leaders. In the observations made by doctors in training, no differences in leadership were found between specialized and primary healthcare.

**Conclusion:** The assessments on good medical leadership support the concept of transformative leadership in healthcare organizations. It would be important to promote further discussion and solving of leadership challenges during specialist training. Furthermore, the role played by the leaders of young physicians trained in healthcare organizations and the management skills of these doctor leaders is also an important topic to consider.

**Key words:** Doctor Leader, management skills, doctor in training

## Introduction

This article describes perception about doctor leaders' medical leadership and management skills, made by specializing physicians during their clinical training in primary and specialized healthcare.

### *To be a good doctor and leader*

In hospitals and clinics, many aspects of physicians' daily routine have changed dramatically during the past generation, adding another level of complexity to the management of healthcare (1).

Medical leadership is at the core of health reforms in a number of countries when policy makers acknowledge that delivering the desired improvements in healthcare, including quality, safety and value, is very dependent on doctors and their active engagement (2). In parallel with political and organizational change, the medical profession has been redefining the characteristics of a good doctor. This includes not only the reinforcement of the need for doctors to be clinical experts but also the not so obvious need for them to be good managers and leaders (1, 2, 3).

Healthcare organizations pose specific leadership challenges for several reasons. Firstly, as organizations they are complex, usually characterized by multi-level professional workforce and silos or freedoms of specialties (4, 5). Secondly, characteristics of physicians and their training conspire against their having reflexes for collaboration or followership: these are needed for effective teamwork that leaders must harness for ensuring positive organizational change (6). Thirdly, the demands of medical training and academic settings, of developing academic skills and performance, often compete for physicians' attention and, thereby, potentially handicap the development of

leadership skills. Finally, healthcare today faces a number of pressing challenges regarding access, affordability and quality (7). Considerable evidence supports the notion that leaders and their actions affect organizational results (8).

While several studies in recent years have sought to identify factors that promote effective physician leadership (9-13), limited focus has been put on understanding how doctor leaders themselves construe their roles. The typically dual role of physicians as both consumers of healthcare resources and controllers of organizational revenues in their ability to direct patients and prescribe care, makes leadership relationships with physicians fairly atypical in comparison with key stakeholder relationships in other industries (14).

In an interview study, Quinn sought to find out how doctor leaders themselves construe their roles, by interviewing 25 physicians in four hospitals within a single healthcare organization. Findings suggest that identity at individual, relational and organizational level has a significant impact on how physicians understand and enact leadership, and that acceptance of a dual identity may be advantageous for success as a doctor leader (15).

As doctors progress through their training a classification process is thought to occur: they are not only learning how to become doctors and care for patients, but also being socialized into a profession and assuming their identity as physicians (16). When they, then, move on to leader roles the majority of physicians hold on to their primary identity (17). The value of their identity as doctors lies in their expertise which has been reinforced through their professional group (15).

With a few exceptions, not many doctors have been prepared for their leader roles, whether as practitioners or those who assume positional leadership roles. Large part of their development as leaders has been remedial, episodic and ad hoc. Yet, from the moment they graduate, doctors require a range of leadership and service improvement competencies which become more important as they go forward to become consultants and general practitioners (2).

Traditionally, clinical skills have been the main focus of medical training. However, with the growing trend towards more team-based practice and integrated care approaches, it is recognized

that doctors need to be safe, capable practitioners and demonstrate skills to function efficiently and effectively within complex health systems (18).

### *Medical leadership*

Medical leadership has only recently begun to assume its place in common medical terminology. Medical leadership consists of having fully trained physicians occupying leadership roles relevant to practice of medicine. Leadership can include managing resources, making decisions, recruiting and medical consulting, as well as implementing changes and improvements in hospitals and clinics. In addition, medical leadership should include appropriate skills in team building and sharing of decision power (19).

From this perspective, there is no room for all-powerful leaders who have nothing in common with the team they are managing. Good medical leadership depends on the acknowledgement and the understanding of how important role all the healthcare workers involved in the functioning of a hospital have (19). Stoller has suggested four features of doctors and medical training that may conspire against their having instincts or reflexes to collaborate: physicians 1) go through a long and hierarchical training often with extended subordination, 2) they are extensively evaluated, usually based on individual performance rather than group or team-based performance, 3) they may experience extrapolated leadership in which they extend the clinical authority that is conferred to them by patients to settings for which it is irrelevant, and 4) they are deficit-based thinkers, specifically because differential diagnostic thinking encourages physicians to identify problems (6).

Prior to the specialist training, physicians in training have worked as doctors in different areas of healthcare for a certain period of time and have been strongly socialized into the profession. During their career they have come across different kinds of doctor leaders, especially during the final years of clinical training when their manager is often also their tutor for clinical work. Leadership and management studies during the specialist training are aimed at supporting physicians' knowledge and skills on the most important issues related to leadership.



### ***Leadership skills***

There is much debate on the nature and components of management and leadership skills. Various competences and lists of required skills are presented in studies. Recently, researchers have emphasized that good leadership must be transformational, requiring leaders to be able to empower and motivate their workforce, define and articulate a vision, build and foster trust and relationships, adhere to accepted values and standards, and inspire their team members to accept change and meet organizational goals on multiple levels (14, 20).

The scope of their professional activities requires physicians to be good team leaders. In fact, doctors working in clinics as well as in hospitals lead small groups of healthcare professionals on a daily basis. While the teams may seem small, physicians nonetheless need to demonstrate essential leadership skills. When they work in large hospitals they also have to be able to appropriately execute directions issued by their superiors to ensure smoothness of inter-staff relationships and the well-being of the hospital environment. Most doctors are constantly involved in situations where they need to be both able to manage and be managed (1).

In interviews of ten academic internal medicine chairs, several critical leadership success factors were identified, including mastery of visioning, communication, change management, emotional intelligence, team building, business skills, personnel management and system thinking (10).

After studying the leadership skills of young aspiring physician leaders and experienced physician leaders, Taylor et al. have proposed four general competences for effective physician leaders: knowledge, emotional intelligence (defined as self-awareness, self-regulation, motivation, empathy and social skills), vision, and organizational altruism. Good personal characteristics were considered to be charisma, ability to create vision, being energetic, taking care of others and being empathetic (13). Both aspiring and established leaders agreed that knowledge, people skills or emotional intelligence and vision were all characteristics of effective leaders and critical for the success of aspiring leaders. In addition, established leaders mentioned organizational orientation as a characteristic; this extended the description of leaders to

include an understanding of the institution as well as dedication to its success.

Stoller has suggested six domains of needed competence for characterizing effective physician-leadership: these include technical knowledge (of operations, finance and accounting, information technology and systems, human resources, strategic planning, and legal issues in healthcare and public policy), knowledge of healthcare (reimbursement strategies, legalization and regulation, quality assessment and management), problem-solving process (around organizational strategy and project management), emotional intelligence (ability to evaluate oneself and others and to manage oneself in the context of a group), communication (leading change in groups and in individual encounters), and commitment to lifelong learning (7). The Leadership Competences questionnaire for physicians in 2002 surveyed 110 doctor leaders to find their top three competences: interpersonal skills, professional ethics and social responsibility, and financial acumen and resource management (21).

With the increasing need for medical leadership comes the need to increase leadership and management training for physicians and to better define roles and responsibility (3, 22-24).

There is an increasing will to see doctors take on more significant leadership roles in the delivery of high-quality healthcare and improve efficiency of healthcare organizations and systems. Leadership skills are essential tools for all doctors throughout their training careers (25). The aim of the training is to enhance e.g. strategy sharing skills, financial skills, organizational knowledge, networking and planning skills (13), as well as skills needed for change management (22).

In this study, we aim to answer the following questions: 1) What factors are seen as important in the medical leadership of clinical work in specialized and primary healthcare units, by doctors in training? 2) Which management skills are valued in physician leaders by doctors in training?

### **Materials and methods**

This study was carried out during leadership and management studies of specialist training of doctors. In Finland, the specialist degree in medicine is classified as specialized postgraduate de-

gree. It can be undertaken at five university medical faculties in Finland.

To complete the specialist degree, 5 or 6 years of medical practice is required including, at minimum, 9 months of service in public health centers, theoretical courses, management studies, and successfully passing a national written exam. The national curriculum for the specialist degree includes theoretical multi-professional social and health management studies (10-30 ECTS). These studies offer the basics of organizational management and leadership, the social and healthcare system, HR management, leadership interaction and organizational communication, healthcare economy, and data administration.

Data for this study was collected in autumn 2012 and spring 2013, as part of leader-member interaction and organizational communication module of specialist degree leadership and management studies. The program of the module was based on pre-reading material, lectures (contact learning), and an essay (distance learning assignment).

Students were asked to reflect on and write an essay about their observations and experiences of leader-member interaction and communication practices in healthcare organizations. Essays were handed back to the lecturer for comments via online learning environment. Finally, every student with an approved paper received brief qualitative feedback. A written permission was obtained from the students to use their essays as research material. Although the topic for the essays was primarily people management and interpersonal skills, in addition substantial data on organizational management in general and challenges related to different operating environments also became available.

The total number of returned essays was 204 in 2012 and 22 in 2013, in total 225. All the essays were merged and then classified into two categories: papers describing communication in hospital organizations (hospital essays,  $n=120$ ), and papers describing healthcare centers (healthcare essays,  $n=105$ ). Finally, altogether 60 hospital essays and 60 healthcare essays were highlight for the data. In the order of arrival, every other essay was taken for the data, thus ensuring that they represented as widely as possible the different kinds of organizations and fields of specialty. The data represents both specialized and primary healthcare as well as large

and small organizations in a wide geographical area. The length of the essays varied from three to seven pages. Some of the writers of these essays had experience of working as a doctor before their specialist training and almost all had experience of several training posts during their specialist training.

The research questions were analyzed by inductive content analysis (26). The data was first read through multiple times to get an overview. In this first phase, we looked for content related to observations made by doctors in training about leadership and management in the training organization. We used phrase as the unit of analysis. Original phrases were picked out from the data word-for-word after which they were reduced, categorized and coded by keywords describing the content. There were in total 325 reduced phrases, 184 on specialized healthcare and 141 on primary healthcare. In the next phase, these phrases were categorized based on similarities and differences. Phrases with similar kind of content were grouped into sub-categories and further abstracted into main categories. The categories were coded by keywords describing their content: personal characteristics of leader, approach to employees and their work, and management skills (26, 27).

## Results

In the results of this study, several different observations on the management skills and leadership of doctor leaders were highlighted by the specializing physicians. The data consisted of 325 individual phrases out of which 185 were related to medical leadership in specialized healthcare and 141 to leadership in primary healthcare.

Regarding good medical leadership and its characteristics, no differences were found in the data between specialized healthcare and primary healthcare. However, deviations were detected between different operational environments of organizations and challenges arising from these different settings. Regarding specialized healthcare in general, strong hierarchy within organizations and between professions, as well as the division of labor, were seen as challenging. According to doctors in training, these challenges made their work more difficult and affected their motivation and wellbeing at work. In primary healthcare,

more challenges arose from mastering the wide range of illnesses of patients and inhabitants of the municipality and from the complex networking nature of the work. It was seen that the ability and skills to work efficiently in a network consisted of multi-professional work, collaboration between different sectors within a municipality (social and health services, schools, prenatal clinics), and co-operation with municipal policy makers. These results have been studied elsewhere.

The framework of the results was three-fold: managing expertise, managing the work community and leader-member relationship. From the observations made by doctors in training, three main themes could be established for ensuring good medical leadership: leadership skills in managing medical expertise, people management in the work community, and interpersonal and communication skills. This framework is described in Figure 1. For each of the three main themes in Figure 1, five most important issues are listed in order of emphasis (Figure 1). Same things were emphasized in leadership of both specialized and primary healthcare.

### Management of expertise

When good medical leadership of clinical work in a healthcare unit was assessed by doctors in training, clinical know-how of doctor leaders was emphasized the most; how leaders themselves were as physicians and, moreover, how these experienced senior physicians gave consultation and guidance to young specializing physicians. Part of the clinical skills of doctor leaders was also their ability to give constructive feedback on the actual patient work to the doctors in training did, as well as feedback during development discussions concerning the general progress of the young doctors. Specializing physicians wanted development discussions to concentrate on the development of their professional expertise and know-how. Leadership skills of doctor leaders in the organization were strongly linked with their clinical skills.

*"My view is that in organizations consisting of doctors, also managers should be doctors so that they can understand and give support in work-related challenges. In a hospital environment managers should be clinically experienced physicians; this way they can keep up with everyday routines and have a point of view on the ever-changing challenges of this work" (Essay 35)*



Figure 1. Good medical leadership assessed by doctors in training



In addition to clinical know-how, doctor leaders were expected to be persons who knew what went on in the organization and who communicated information within the organization. They were expected to have an extensive network of colleagues both within and outside the organization. Furthermore, doctor leaders were expected to have a vision on the future and ability to guide the organization in changes).

*"It is the managers' task to know what goes on in the organization. Openness and sufficient communication can be expected of them as a default, as well as good rationale behind all decisions concerning the whole organization. The management style where a leader just tells things to employees without listening to their views and without giving any background for decisions is not a suitable model for managers who are leading a team of experts. Managers should share their views and plans about the future in a truthful and appropriate manner. Also, in uncertain situations and during changes in the organization managers should show boldness and openness with regards to supporting communications between employees"* (Essay 12)

### HR-management

What was also expected of doctor leaders was the ability to manage the work community and handle any people management related issues. Furthermore, in management of clinical work, emphasis was put on the fact that doctor leaders should take into account all employees in their unit and know what their work consists of. The most important things in the relationship between doctor leader and their employees were overall support given to employees, appreciation of professionalism and taking care of wellbeing at work. It was also seen important that the unit was managed fairly and in a just manner.

*"In my unit there is an especially good leader who allows different ways of operating, but still oversees that the quality of work remains good and things get done. If there is cause to trust employees he trusts them. He also listens to my views. It is important to him that I can also have time off*

*during the holiday seasons even though I'm just a trainee. At work, everyone is treated equally. There are yearly development discussions where I can share my views on anything related to work and plan my further training"* (Essay 52)

*"Expertise and fairness are essential leadership skills. When an employee feels that he is appreciated by his manager and is treated justly and when the manager is interested in his employees, the wellbeing of the whole unit increases. It is important that the manager appreciates and values the work his employees are doing. Respect and good manners are contagious, and the manager should be an example for all. Also, all employees no matter which position they work in should be taken into account - everyone's work is valuable"* (Essay 13)

### Interpersonal and communication skills

Regarding the interpersonal and communication skills of doctor leaders, specializing physicians emphasized building of positive relationships based on mutual trust. A good relationship based on trust allows the doctor in training to share things from their personal life with their manager when needed. All trainees highlighted the importance of interpersonal and conversational skills of managers, as well as approachability and availability when guidance and consultation was needed. An ideal leader was seen as a senior 'father figure' who has the time and willingness to listen and guide his young colleagues. Also opposite observations had been made by doctors in training.

*"My manager is interested in my wellbeing also outside work and, if needed, it is possible to flexibly arrange work so that I can handle both home and work"* (Essay 52)

*"Our chief physician takes care of our wellbeing and is an approachable, warm and humane person. She has a long career in clinical work and is a good colleague who I can always consult. She does not keep up levels of hierarchy just for the sake of it. From my point of view, I see it as a huge benefit that she has worked so long in our municipal health clinic and knows the organization and the people who live here. She is on our side and means well in everything she does. I like her straightforward no-nonsense attitude"* (Essay 26)

*"The chief physician is really not that much in contact with us employees. I've seen him about three times during the past four years in our quarterly doctors' meeting. Any e-mails he sends usually go to the heads of department, who in turn forward these e-mails to us. The division of labor between heads of department, deputy chief physicians and the chief physician is not clear, as far as I can tell. Whenever I face some problem I am often not sure whom I should notify so that it could be solved"* (Essay 15)

*"Working in a clinic is lonely and positive feedback is seldom received. Even negative experiences with patients cannot usually be shared with anyone during normal clinic work. In this kind of situation, it would be good to get support from manager"* (Essay 12)

## Discussion

Medical leadership takes many forms. Some physicians lead through local innovation, others lead through their professional bodies or through managerial involvement at various levels in the organization. Successful doctor leaders are usually experienced clinicians with good interpersonal skills. They are also strategic thinkers and visionaries who look beyond the boundaries of their own field of speciality; they exhibit passion and are prepared to take reasonable risk to achieve their goals. They know how to engage colleagues and effect change (28). What became apparent in the observations on leadership made by doctors in training was the versatile and wide experience of managers - it was respected and valued.

In their writings on medical leadership what specializing physicians emphasized the most were things that were closest to them and their daily work. The idea of good leadership was formed mainly based on personal experience from either one or several clinical training posts. As apprentices, doctors in training deemed important the interpersonal communication skills, especially social support skills, of their managers. These are also the skills they can best assess: How a leader expresses understanding and person-centeredness seems to be an important factor when evaluating the quality of leader-member relationship (29). The descriptions of medical leadership by doctors

in training were similar to descriptions of transformative leadership in healthcare organizations. Emphasis is put on communication, motivation, visioning, mutual trust and values (14, 20, 30). When assessing good medical leadership, financial know-how, knowing the organizational culture, strategic skills, ability to manage knowledge etc. were not highlighted as important (7). These skills may be too far from the everyday work of a doctor in training and would require longer time to be fairly assessed (31). The reason could also be that specializing physicians have emphasized leadership and communication practices of their unit in their essays based on the task they were given. All in all, the results of this study offer a sufficient framework for good medical leadership, adaptable also for management of experts in other fields of specialty.

In some of the essays the writers showed interest in discussing leadership and management skills in a wider context. This is a good thing as it will motivate them to take the leadership and management studies of their training seriously and, therefore, develop their own leadership skills throughout their training with their future leader position in mind. When we offer young doctors new and various opportunities to practice leadership and work as leaders we enhance their motivation to further pursue managerial positions.

The concept of medical leadership should not be limited to those in senior leadership positions. It is just as relevant to the trainee doctor on the frontline who uses leadership skills to run the ward in the absence of a consultant or to set up a quality improvement project to improve the weekend handover. A medical leader can be any leader who uses leadership skills to improve the care they provide to patients (8). There is an increased need for leadership training for both young and senior physicians (3).

The importance of the support given by senior physicians to young doctors cannot be emphasized enough. Doctor leaders receive both good and critical feedback on their management skills. It would be beneficial to develop a discussion forum where mentors and managers of doctors in training could meet and discuss the role of doctor leaders in relation to specializing physicians, and what kind of expectations and wishes young doctors have towards their managers and leadership.

Leading specializing physicians brings a new dimension to the work of senior physicians: this dimension could be called pedagogic leadership.

### Acknowledgments

This study has received partial funding for one researcher from the Finnish Cultural Foundation.

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 Publisher: DRUNPP Sarajevo  
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# Two case of Rhinolitis which discovered by functional endoscopic sinus surgery

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## Abstract

The introduction of functional endoscopic sinus surgery beside the medical therapy for chronic rhinosinusitis made the interventional procedures competent. In this study we reviewed two cases of rhinolitis which were discovered and removed by functional endoscopic sinus surgery. The outcome of these two cases revealed that patients' pain decreased and patients were satisfied with functional endoscopic sinus surgery.

**Key words:** functional endoscopic sinus surgery, rhinolitis, maxillary sinus

## Introduction

Prior to 1985, surgical intervention for sinus disorders included external procedures, often needing an incision on the face. To approach the maxillary sinus, a Caldwell–Luc incision (made in the gingivobuccal space) was used to make a window in the anterior wall of the maxillary sinus. A Lynch incision was made on the face just medial to the medial brow to access the ethmoid and frontal sinuses. More major frontal sinus disorders often included a bicoronal incision, which extended across the scalp in the coronal plane from ear to ear.

These external procedures were unsightly and invasive, and therefore, they were a last-resort approach to recalcitrant sinus disorders (1, 2, 3).

Since the early development of functional endoscopic sinus surgery (FESS), this minimally invasive technique has obtained increasing popularity among otorhinolaryngologists (2,3,4,5,6). In the current study we indicated two case of rhinolitis which discovered by FESS.

## Case 1

22 year old woman with chief complaint of epistaxis referred to otorhinolaryngology section of the university hospital, Mazandaran University of medical sciences, Sari, Iran, 2014. Otherwise the patient has sputum and post nasal discharge. In the past medical history the woman had headache for four years.

During FESS the rhinolitis was discovered in ostiomeatal complex and orifice of right maxillary sinus and the pathology of ethmoid and maxillary sinuses showed acute on chronic rhino sinusitis.

## Case 2

A 12 year old boy with chief complaint of nasal discharge during one past year with sputum. In the examination cold well X ray showed ethmoid sinus inflammation. Pathology of right maxillary sinus and ostiomeatal complex indicated chronic rhinosinusitis with rhinolitis. Patient underwent FESS and rhinolitis was found on septum and orifice of maxillary sinus.

## Discussion

During past years fess has been used for treatment of paranasal sinus diseases (4-6). Many investigations have reported symptomatic and radiographic achievement of sinus disorders by FESS in 76% to 87.5% of patients observed 1 to 3 years after the surgery (6,7,8). Even recent researches revealed asthma improvement after FESS in children (9,10,11,12,13).

These two cases showed that for complicated headache and prolonged nasal discharge FESS could be the solution. The outcome of these two cases showed the patients' pain revealed and patients were satisfied with FESS.

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# Assessment of the maximal respiratory pressures in chronic kidney patients submitted hemodialysis treatment

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## Abstract

**Introduction:** Chronic renal failure (CRF) is a pathological condition that causes many complications, among them changes in respiratory muscle function. These changes can be assessed by measuring maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP). We evaluated maximal respiratory pressures in CRF patients who perform hemodialysis.

**Methods:** We conducted a cross-sectional analytical study, which evaluated 24 patients with CRF receiving hemodialysis treatment. We evaluated MIP and MEP immediately before and after hemodialysis.

**Results:** We observed that 16 were male and mean age was  $56 \pm 14.81$  years. Almost all of them 23 had an arteriovenous fistula, 9 were hypertense and 6 were diabetic. Both MIP and MEP were below predicted values for individuals of the same age ( $p=0.01$ ). Comparing values pre and post hemodialysis, MEP showed a slight improvement ( $p=0.01$ ).

**Conclusion:** CRF patients on renal replacement therapy showed a significant reduction compared to the predicted value of maximal respiratory pressures.

**Key words:** Chronic renal failure; Hemodialysis; Muscle Strength; Respiratory.

## Introduction

Chronic renal failure (CRF) is currently a public healthcare problem<sup>1,2</sup>, due to the increase in

cases worldwide related to the higher prevalence of chronic diseases such as hypertension and diabetes mellitus, and also associated to aging population trends<sup>3-5</sup>. The number of cases of CRF increases each year. In our country, in 2004, more than 58,000 cases of kidney failure have been diagnosed and, in global terms, it is estimated that more than 2,000,000 patients are in dialysis treatment programs<sup>4</sup>.

Characterized by a set of nephropathy-related symptoms, CRF is a pathological condition leading to progressive and irreversible loss of renal function, finally compromising hemodynamic stability<sup>6</sup>. Among these changes are atrophy and loss of skeletal muscle strength, weight loss, edema, fatigue and skin discoloration. Additionally, there are also clinical manifestations as rash, anorexia, nausea, vomiting and hiccups, changes in level of consciousness, seizures, muscle contractions and hypertension, which leads to heart failure and pulmonary edema<sup>6</sup>.

One can also appreciate changes in the respiratory system due to the excess serum urea and due to poor or no renal filtration<sup>7</sup>. Due to this pulmonary compromise, there is a ventilatory deficit that can be measured through changes in vital capacity as well as decreased respiratory muscle strength<sup>5</sup>.

Hemodialysis (HD) is a treatment that has the function of performing the filtration of blood through a semipermeable membrane that is responsible for the separation between large particles (such as blood cells) and small particles, among which the-

re are urea and other toxic products that were previously eliminated in urine<sup>8</sup>. In order to have blood filtered and returned to the body a vascular access needs to be created. Arteriovenous fistula, one the commonest vascular accesses being performed in an operating room, consists in a subcutaneous anastomosis of an artery with an adjacent vein, usually in the non-dominant upper limb<sup>9</sup>.

However, treatment of HD patients are prone to changes regarding the biochemical composition of all body fluids, causing changes in volume, and directly affecting the mechanics and respiratory muscle function<sup>1</sup>. Changes affecting respiratory muscle strength are measured through maximal inspiratory pressures (MIP) and maximal expiratory pressures (MEP), recorded by a manovacuometer. These measurements can assist in the evaluation of critical patients<sup>1</sup>.

This study aimed to evaluate maximal respiratory pressures in CRF patients who perform hemodialysis.

## Method

This cross-sectional analytical study was conducted after approval of the Ethics Committee of the Universidade Cruzeiro do Sul. The survey consisted of 24 patients with CRF who were treated in the hemodialysis unit of Hospital e Maternidade Assunção, located in the city of São Bernardo do Campo.

Patients of both genders were included, ages 20 to 83, who agreed to participate. Prior to assessment all patients signed an informed consent form (protocol number 338/082 012). Exclusion criteria were not willing to participate in the study as well as not being able to complete the second evaluation (after HD). Patients were oriented with respect to the research protocol and they also took part in an evaluation containing personal and clinical data.

Tests were conducted with patients who performed three weekly dialysis sessions lasting four hours each session, and the first, second and third sessions made on Monday, Wednesday and Friday respectively. Measurements of MIP and MEP were performed only once in the pre and post dialysis in the first session of the week, so after 3 days of the last session of hemodialysis.

Analysis of respiratory muscle strength was performed by measuring MIP and MEP through an analog manovacuometer (Commercial Medical® / M120 / São Paulo, Brazil) capable of measuring positive and negative values with a range from -300 to +300 cm H<sub>2</sub>O. It was connected to a semi-flexible plastic transparent tube, ending in a white cardboard disposable mouthpiece. First, patients were instructed regarding the measurement technique after they were seated on a chair, remaining seated in an angle of 90°. A nose clip was employed to occlude the nostrils; the patient was instructed to hold the mouthpiece against the face and to hold the nozzle with the teeth to prevent air leakage.

For the evaluation of maximal inspiratory pressure (MIP), the patient was asked, through verbal command, to perform a slow and complete exhalation until the residual volume (RV) and then perform a maximal inspiratory effort and hold for 2 seconds, when data was obtained. For maximal expiratory pressure (MEP), the patient was asked to inhale the air completely until total lung capacity (TLC) and then performed a maximal expiratory effort in the nozzle connected to the manovacuometer<sup>10</sup>. Each measurement was repeated three times, with breaks for rest, and only the highest obtained value was considered. All this procedure was performed before and after the hemodialysis session<sup>11</sup>. In the present study, the values of MIP and MEP were compared with the values predicted by the formulas presented below<sup>12</sup>: MIP- Women:  $-0.49 (\text{age}) + 110.4$ ; standard error of the estimate = 9.1; Men:  $-0.80 (\text{age}) + 155.3$ ; standard error of the estimate = 17.3. MEP-Women:  $-0.61 (\text{age}) + 115.6$ ; standard error of the estimate = 11.2; Men:  $-0.81 (\text{age}) + 165.3$ ; standard error of the estimate = 15.6.

Statistical analysis of maximal inspiratory and expiratory pressures, with data presenting normal distribution, was conducted using ANOVA and Tukey *post hoc* test calculated in Graph Pad Prism 5 for Windows. We used the non-parametric statistical analysis, and the results were presented as mean and interquartile range (II). Analysis of spirometric and maximal respiratory pressures before and after hemodialysis was performed using the Wilcoxon test. Correlations were evaluated using the Spearman correlation coefficient. All analyzes were as significance level  $p < 0.05$ .

## Results

We studied 24 subjects (16 were male). Mean age was  $56 \pm 14.81$  years (range: 22 to 83 years), mean post-dialysis weight was  $70 \pm 14.06$  kg (range: 45-110 kg) and the time interval during which the patient had been treated with HD was  $33 \pm 28.61$  months (range: 1-108 months). Table 1

Regarding the venous access type, 23 of these patients had an Arteries Venous fistula, 7 located in the right upper limb, 14 in the left upper limb and 2 elsewhere. In this sample, only 1 had a venous catheter.

The prevalence of associated diseases in this sample is detailed in Table 2.

Regarding maximal respiratory pressures, we compared the sample results before and after hemodialysis, and also with predicted values [11]. Significant changes were observed in MEP values for males ( $p < 0.05$ , Table 3) (Figure 1 and Figure 2).

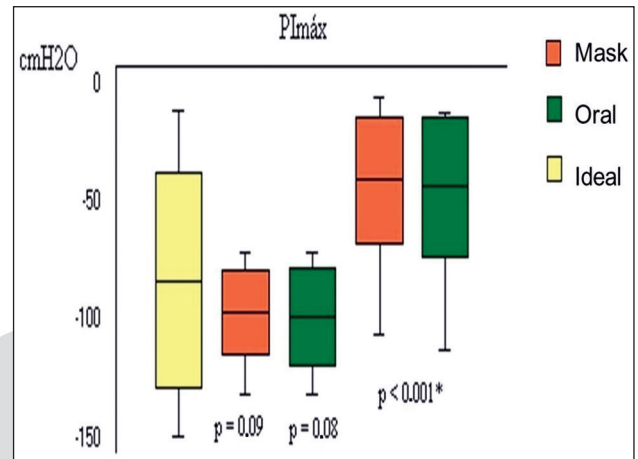


Figure 1. Values of maximal inspiratory pressure. Mask: Test with the mask; Oral: Test with the mouthpiece; Ideal: control. \* $p < 0.05$ : Vs. predicted

Table 1. Anthropometric data of the subjects

Age (years)	Weight before hemodialysis	Weight After hemodialysis	Treatment time (months)
$56 \pm 14,81$	$66 \pm 10,90$	$70 \pm 14,06$	$33 \pm 28,61$

Table 2. Associated diseases in the study population

Associated diseases	%
Arterial hypertension	39.3
Diabetes mellitus	25.0
Arterial hypertension and diabetes mellitus	16.6
Kidney Diseases (as Glomerulosclerosis and Pyelonephritis)	8.33
Neurological diseases (stroke and neurogenic bladder)	4.16
Cardiac diseases (AMI and CHF)	8.33
Oncological Diseases (renal cell tumor and lymphoma)	8.33
No illnesses associated	4.16

Legend: AMI = acute myocardial infarction and CHF = congestive heart failure.

Table 3. Mean values and standard deviation of maximal respiratory pressures before and after hemodialysis (HD)

	Pre HD	Post HD	p
<b>Female</b>			
MIP	$-75.63 \pm 10.92$	$-75.00 \pm 14.02$	0.47
MEP	$55.63 \pm 5.85$	$56.25 \pm 4.80$	0.46
<b>Male</b>			
MIP	$-80.63 \pm 6.24$	$-86.88 \pm 6.12$	0.17
MEP	$81.88 \pm 5.68$	$90.31 \pm 5.44$	0.01

Values expressed in cm H<sub>2</sub>O. \* $p < 0.05$ . Legend: MIP = maximal inspiratory pressure; MEP = maximal expiratory pressure.



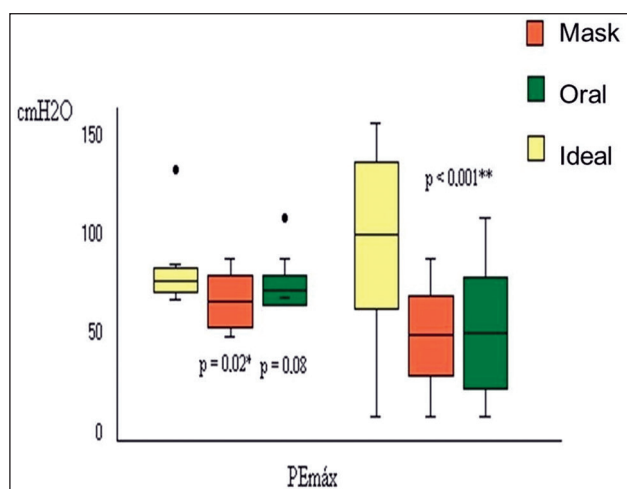


Figure 2. Measurements of maximal expiratory pressure - MEP with mask or mouthpiece compared with the control group in 10% of the sample that had values within the normal range (\* $p = 0.02$ ) and in 90% of the sample which showed lower values to normal values ( $p < 0.001$ ). Mask: Test with the mask; Oral: Test with the mouthpiece; Ideal: control

## Discussion

This investigation was undertaken to evaluate maximal inspiratory and expiratory pressures in CRF patients under hemodialysis. We reported significant changes in MEP values for males and it was also noted that both MIP and MEP were decreased compared to the predicted values. On the other hand, MEP was significantly lower compared to the predictive values.

Average age among individuals in this sample was similar to that found in the study of Coelho et al<sup>13</sup> whose sample included patients with CRF. Male predominance also is in agreement with the literature<sup>14</sup>; besides, data from our country demonstrate that males represent the majority of patients in renal therapy, about 57% of cases<sup>4</sup>.

Unlike Cherchiglia and colleagues<sup>4</sup>, who found in their study that only 10% of patients started dialysis with a permanent vascular access, indicating some difficulty in access to nephrologist care, our study showed that 23 of the sample had an Arteriovenous fistula, since the patients evaluated were accompanied by medical staff since the beginning of treatment.

Despite being a unique sample, comprising 24 young adults and elderly patients, it was observed

that there was a significant decrease compared to the predicted values of maximal respiratory pressures. The present study corroborates the work of Jatobá et al<sup>15</sup>, where decreased muscle strength was detected, obtained through MEP and MIP measurements in patients undergoing renal replacement therapy compared to normal individuals.

CRF and hemodialysis affect the respiratory system. Muscle weakness is one of several complications presented by chronic kidney patients<sup>1</sup>. According to some authors<sup>16</sup>, hemodialysis promotes the degradation of muscle proteins as well as in the entire body, suggesting a strong involvement of the respiratory muscles.

MIP was reduced after hemodialysis sessions, both in the current work, as well as in other studies<sup>17</sup>. There are few studies evaluating respiratory muscle strength and performance in patients on renal replacement therapy, but they agree that the therapy is vital to the patient, and it does not seem to cause immediate or delayed damage to respiratory muscle performance. Briefly, the results obtained in our study along with others showed that hemodialysis may have variable effects on respiratory muscle strength, since one can appreciate little or no improvement, or even worsening<sup>18</sup>.

MEP in males, for example, showed an improvement between pre and post-dialysis values. This finding has not been detected before as statistically significant, and it is very important considering that MEP refers to the strength of the expiratory muscles, which are responsible for instance for the coughing mechanism, extremely necessary for every individual.

Learson evaluated the performance of the MIP and found significant improvement in learning in patients with COPD, after a training technique for 4 weeks<sup>19</sup>. In our study the improvement of muscle strength is not related to learning the technique because they only performed it once in a single session in the pre and post hemodialysis.

As a main finding we indicate that hemodialysis can provide some improvement in this regard, as MEP increased after the procedure. This fact demonstrates the improved function of the expiratory muscles, which are mainly responsible for the cough mechanism.

Our data suggests that the reduction in the strength of the muscles is progressive and can be

aggravated by the disease and the greater the interval between sessions of hemodialysis. Considering this decrease in a heterogeneous group, all subjects showed tendency to reduce muscle strength. Muscle strength increased after dialysis for all patients, i.e. all the strength they lost in just 3 days without dialysis, and it returned to normal baseline values, whereas these variations in muscle strength always occur in this group of normal patients were not found patients with lower values of respiratory muscle strength. The weakness of the respiratory muscles indicates pulmonary changes that can be observed in different diseases in individuals with renal failure<sup>20</sup>. This decrease in strength may be associated with dysfunction of the kidneys in fluids and electrolytes remove causing overload for these muscles responsible for respiration. The situation may be further exacerbated in bedridden or hospitalized under these conditions.

The fast improvement in muscle respiratory strength may be related to weight loss<sup>21</sup> increasing weight in dialysis patients, worsening respiratory muscle strength and this can be reversed by dialysis. The respiratory muscle strength decreases with increasing on dialysis. The progressive loss of renal function leads to injury in several systems and patients on hemodialysis treatment for a long period to evolve alterations of the respiratory system such as decreased strength and endurance of respiratory muscles<sup>22</sup>.

One limitation of this study is the absence of spirometric tests to make the differential diagnosis of chronic obstructive pulmonary disease and allowing us to better analysis the respiratory functions before and after dialysis. Also, we did not evaluate body mass index, all patients were weighed once before the dialysis. We did not aim to evaluate the degradation of muscle strength in chronic respiratory disease over time to evaluate its evolution, we suggest further studies to investigate this issue.

## Conclusion

The evaluation of patients with CRF on hemodialysis demonstrated a significant decrease of maximal respiratory pressures compared to predicted values. Hemodialysis proved important because it influenced positively the outcome

of MEP, denoting improved function of the expiratory muscles, the main responsables for cough mechanism. Further studies might deepen the knowledge on respiratory muscle function in patients affected with chronic kidney disease in hemodialysis therapy.

## Authors' contributions

All authors participated in the acquisition of data and revision of the manuscript. All authors determined the design, interpreted the data and drafted the manuscript. All authors read and gave final approval for the version submitted for publication.

## Acknowledgements

This manuscript received financial support from UNESP. The funding body provided financial support to make all procedures and in the decision to submit the manuscript for publication.

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# Massive thyroid follicular adenoma: a case report

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## Abstract

During past decades there was an increase in the incidence of thyroid cancer. In the current study we reported the massive thyroid follicular adenoma with recurrent laryngeal nerve involvement. The microscopic examination showed that benign encapsulated thyroid glands with small follicle with colloid inside it. The patient underwent resection of the tumor with neck dissection.

**Key words:** thyroid, follicular adenoma

## Introduction

During past 30 years there was an increase in the incidence of thyroid cancer and a study showed the prevalence of this malignancy in females and males 67%, 48%, respectively in the world (1).

The incidence of thyroid cancer is higher in females than in males with a ratio of 3: 1, apart from in adolescent and young adult patients where the incidence in women is 5-fold higher (2). In this relation, different ethnic backgrounds and population have showed in various reports (1,3,4,5). Moreover, some studies revealed an increase in small-size tumors (6-8) and some other reports revealed an increase in all sizes (1, 3, 9). Some investigators reported an increase in thyroid malignancy incidence caused by a widespread increase in a still esoteric environmental or lifestyle factor(s) (3, 9-12).

In the current study we reported the massive thyroid follicular adenoma with recurrent laryngeal nerve involvement.

## Case report

A 39 year old woman with chief complaint of neck mass from 9 years ago was referred to otorhinolaryngology section of the university hospital, Mazandaran University of medical sciences, Sari, Iran, 2014. The patient had choking and hoarse-

ness from one year ago. In the past drug history the patient has used levothyroxine. In the exam the mass was not tender but was motile without vascular sound. In the chest CT scan there was multinodular mass in neck with potential necrotic lesions in the center.

## Pathology

The macroscopic feature included brown capsular tissue 16\*13\*10 cm 890 gr which was lobulated and hemorrhagic.

The microscopic examination showed that benign encapsulated thyroid glands with small follicle with colloid inside it.

## Discussion

Follicular adenoma and follicular carcinoma of the thyroid gland are tumors of follicular cell differentiation which included a micro follicular architecture with follicles lined by cuboidal epithelial cells. A follicular adenoma is a benign encapsulated tumor (like this case) of the thyroid gland. It is a firm or rubbery, homogeneous, round or oval tumor that is surrounded by a thin fibrous capsule. In two studies they revealed that the incidence of thyroid adenoma was 3 and 4.3% [13, 14]. The pathology of the current patient was encapsulated thyroid glands with small follicle with colloid.

Follicular carcinoma has two subtype minimally invasive and invasive variants based on morphologic criteria. As we know minimally invasive follicular carcinoma is an encapsulated tumor with microscopic penetration of the tumor capsule without vascular invasion [15, 16].

The current case underwent resection of the tumor with neck dissection.

Shaha in his study reported an overall survival at 5, 10, and 20 years for patients with follicular thyroid cancer of 85%, 80%, and 76%, respectively [17].

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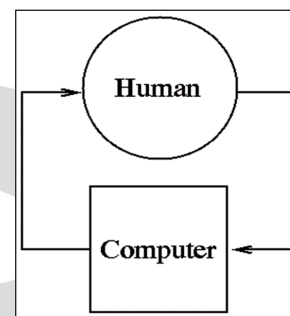


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### Conclusion

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### Acknowledgements (If any)

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