Online ISSN : 2249-4618
Print ISSN : 0975-5888
DOI : 10.17406/GJMRA

Global Journal

of Medical Research: F

Diseases

Cancer, Ophthalmology & Pediatric

Human Immunodeficiency Virus

Obstructive Pulmonary Disease

Highlights

Chronic Lymphocytic Leukemia

Diabetic Nephropatia in Patients

Discovering Thoughts, Inventing Future

VOLUME 19 ISSUE 1 VERSION 1.0

Global Journal of Medical Research: F
Diseases
Cancer, Ophthalmology & Pediatric

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Volume 19 Issue 1 (Ver. 1.0)

Open Association of Research Society

Incorporation No.: 0423089
License No.: 42125/022010/1186
Registration No.: 430374
Import-Export Code: 1109007027
Employer Identification Number (EIN):
USA Tax ID: 98-0673427

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USA Toll Free: +001-888-839-7392
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Offset Typesetting

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Global Journal of Medical Research: F
Diseases
Volume 19 Issue 1 Version 1.0 Year 2019
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Genetic Factors of Diabetic Nephropatia in Patients with Type 2 Diabetes Mellitus

By Ozimbay Jabborov

Abstract- The increasing prevalence of diabetes mellitus has led to a growing number of chronic complications including diabetic nephropathy (DN). In addition to its high prevalence, DN is associated with high morbidity and mortality especially due to cardiovascular diseases. It is well established that genetic factors play a role in the pathogenesis of DN and genetically susceptible individuals can develop it after being exposed to environmental factors. DN is probably a complex, polygenic disease. Two main strategies have been used to identify genes associated to DN: analysis of candidate genes, and more recently genome-wide scan. Great efforts have been made to identify these main genes, but results are still inconsistent with different genes associated to a small effect in specific populations. The identification of the main genes would allow the detection of those individuals at high risk for DN and better understanding of its pathophysiology as well.

Keywords: diabetes mellitus, diabetic nephropathy, polygenic, genome, chronic kidney disease, genetic polymorphism.

GJMR-F Classification: NLMC Code: WJ 340

Strictly as per the compliance and regulations of:

Genetic Factors of Diabetic Nephropatia in Patients with Type 2 Diabetes Mellitus

Ozimbay Jabborov

Abstract- The increasing prevalence of diabetes mellitus has led to a growing number of chronic complications including diabetic nephropathy (DN). In addition to its high prevalence, DN is associated with high morbidity and mortality especially due to cardiovascular diseases. It is well established that genetic factors play a role in the pathogenesis of DN and genetically susceptible individuals can develop it after being exposed to environmental factors. DN is probably a complex, polygenic disease. Two main strategies have been used to identify genes associated to DN: analysis of candidate genes, and more recently genome-wide scan. Great efforts have been made to identify these main genes, but results are still inconsistent with different genes associated to a small effect in specific populations. The identification of the main genes would allow the detection of those individuals at high risk for DN and better understanding of its pathophysiology as well.

Keywords: diabetes mellitus, diabetic nephropathy, polygenic, genome, chronic kidney disease, genetic polymorphism.

I. Introduction

Recently, the increasing prevalence of diabetes mellitus (DM) is alarming worldwide. For the most part, an increase in the incidence is due to type 2 diabetes, which accounts for 80-90% of all cases of this pathology [26, 31]. The need for an active solution to this problem is dictated by the following unfavorable factors: "rejuvenation" of type 2 diabetes, a significant percentage of mortality disability due to the development of early and late complications of diabetes, like diabetic nephropathy (DN). It is recognized that it is diabetes type 2 the leading pathology, which leads to an increase in the frequency of cardiovascular diseases and vascular accidents in different countries and populations [3]. Gradually developing late complications of diabetes, such as retinopathy, nephropathy, polyneuropathy and angiopathy, lead to a significant decrease in the patient's quality of life, and in many cases to severe disability, causing blindness, chronic renal failure, diabetic foot - the main cause of high amputation in patients. Despite the significant progress of the pharmaceutical industry, which led to the appearance on the medical market of a wide variety of high-quality pharmaceuticals, the number of patients who do not reach the recommended treatment goals remains high. The unfavorable situation with type 2 diabetes predetermined the development and adoption in 2007 of common international treatment approaches. By decision of the 2007 consensus, the target level of glycated hemoglobin should not exceed 7%. For the first time, the need was indicated for the prompt and timely correction of the treatment regimen in the long-term absence of a decrease in glycated hemoglobin to non-diabetic values [3, 10, 11].

Subsequently, it was noted that achieving compensation for diabetes mellitus and stable maintenance of the target values of glycated hemoglobin prevents the development of late complications in all patients. The study of this controversial situation led to the possibility of genetic justification of the predicted complications. Since diabetes mellitus type 2 is not a genetically mediated disease, its debut and progression up to the development of complications are associated with many genes and their complex interaction with each other and with environmental factors. The result of new advances in molecular genetics, immunology and some other related disciplines was the development by the WHO Expert Committee on diabetes, taking into account the proposals of the American Diabetes Association, a new, improved classification of diabetes (WHO, 1999). Unlike the previous one, in the new classification the class of "impaired glucose tolerance" was excluded, the name "insulin-dependent" and "insulin-independent" diabetes mellitus for type 1 and type 2 diabetes was changed. In the subsection "Genetic defects of p-cell function", it was suggested include diabetes MODY 1, 2, 3, 4, 5, 6 and some other monogenic types of diabetes, in the pathogenesis of which. The cause of the disease caused by a violation of a particular gene is clearly established. The following types of insulin resistance have been attributed to the genetic defects of insulin: type A insulin resistance, leprechaunism, Rabson-Mendelhall syndrome, lipoatrophic diabetes and some other forms of diabetes resulting from the mutation of the insulin receptor gene [2]. The classification also includes the sections "Endocrinopathy", "Diabetes induced by drugs or chemical agents", "Infection", "Unusual form of immune-mediated diabetes", "Other genetic syndromes sometimes combined with diabetes" and "Gestational diabetes". Thus, the onset of diabetes includes a large number of diseases, which can be divided into diabetes of type 2, genetic syndromes associated with diabetes, and secondary forms of

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diabetes. The proportion of type 2 diabetes accounts for more than 95% of all diabetes, while as the second type in prevalence significantly dominates the first. In spite of the fact that type 2 diabetes develops more often in adult or even old age, there are cases in children. In the development of the disease in childhood, the main importance is attached to the genetic factor. Monozygous twins in 100% of cases are concordant for type 2 diabetes. Parents also in most cases have type 2 diabetes, especially when examined in terms of the glucose tolerance test [1, 2].

Type 2 diabetes is a multi factorial disease, the development of which is due to the mandatory interaction of genetic factors with the environment [2, 9]. However, the genetic basis and degree of importance of various environmental factors in both types are different. For the development of diabetes in both cases, many genes are responsible, i.e. type 1 diabetes and type 2 polygenic diseases. However, unlike type 1 DM, where there is an unfavorable combination of many normal genes, the debut of type 2 DM causes a combination of several pathological genes. It is assumed that type 2 diabetes develops in people who have mutations in the genes encoding the processes of synthesis, secretion and action of insulin [2]. Studies performed (I. I. Dedov et al.) Demonstrated that type 2 diabetes is inherited independently of friend, and nosologically it is an independent disease. The authors concluded that the system of genetic factors determining susceptibility to the two types of diabetes is different. The results of diabetes analysis in the families participating in the study showed that intra-familial similarity in the type of diabetes is largely due to genetic factors, as evidenced by the correlation in the type of diabetes between the probands and their relatives [2]. In the study of families on the subject of heredity according to type 2 diabetes, it was noted that the risk of diabetes in mono-gothic twins is about 70%, in children with one of the parents with type 2 diabetes, about 40%, while in both parents the risk increases to 70% [9, 29]. However, this study does not take into account that environmental risk factors in a given family are similar in nature. For example, brothers and sisters inside the uterine will be subjected to the same effects, which subsequently in the study cannot be taken into account. In other words, with the same genetic set and different effects of unknown environmental factors, the outcome will be different, which may indicate an exaggeration of the role of the genetic component in the development of type 2 diabetes, as assessed in earlier studies [9].

Externally environmental factors, which are the trigger for the development of the disease, also have a fundamental difference. In type 1 diabetes, a viral infection most often serves as a trigger, whereas in type 2 diabetes, lifestyle is fundamental: physical inactivity, improper over-feeding, leading to obesity, bad habits, urbanization, stress, low or high birth weight [2, 9].

Progress in genetics in the 1980s allowed to make attempts to determine the genetic loci that underlie this inherited pathology. Candidate genes, most likely responsible for the development of type 2 diabetes, have been empirically determined based on the pathogenesis and pathokinesis of diabetes. In the course of further research, many candidate genes did not confirm the assigned roles in the development of diabetes. Given the importance of environmental factors and their complex interaction with genes, it may be very difficult to assess the role of a specific genetic component or association of genes in the research.

The difficulty also lies in the fact that, unlike type 1 DM, where candidate genes are mostly concentrated in the HLA region, in type 2 diabetes the mutant genes can be located throughout the genome, increasing the number of different unpredictable variants of their interaction. Modern methods of genetic research, having a relatively low resolution, make it possible to identify genes that have a clear linkage with a specific defect or pathology. This allows you to actively study monogenic diseases, while methods are not quite suitable for identifying genes involved in complex polygenic disorders. Therefore, only two genes that are directly related to type 2 diabetes were identified: calpain-10 (CAPN10) and 7-like 2 transcription factor (T-cell specific, HMG-box) (TCF7L2). About 80% of people are carriers of the calpain gene -10, increasing the likelihood of developing diabetes in humans. Such a high percentage of carriage of the pathological gene and a much smaller number of people with diabetes once again prove the polygenic nature of type 2 diabetes and the undeniable significance of the influence of environmental factors. CAPN10 was the first open gene to have a clear connection with type 2 diabetes. Discovered in 1996 when analyzing the linkage of a locus on chromosome 2, it was originally called the NIDDM1 locus, since specific genes were not identified [7, 9]. In 2000, the CAPN10 gene was identified [9, 17]. The value of the gene in glucose metabolism is still unknown, but many research papers have shown the relationship of this gene with the debut of type 2 diabetes [9]. Calpain-10 is a protein encoded by the CAPN10 gene, and belongs to the family of calcium-dependent cysteine proteases. By organization, it is similar to calpains-5 and -6, being atypical due to the lack of calmodulin in the structure, the calcium binding domain.

The second gene, which has a clear connection with type 2 diabetes, is the TCF7L2 gene, located on chromosome 10. Initially, the relationship of the TCF7L2 gene with diabetes was established in the American, Icelandic and Danish populations. Subsequently, in many studies of GWAS (Genome-Wide Association Studies) in different ethnic groups, the role of one nucleotide polymorphism of the TCF7L2 gene in the onset of type 2 diabetes was proven. Now, the gene

TCF7L2 is the most accurate genetic marker of type 2 DM. GWAS data showed that the risk allele is in the 3rd intron of the gene. The TCF7L2 gene encodes a transcription factor that activates the β-cells of the islets of Langerhans. In studies of V. Lysenko, if there is a risk of an allele in the TCF7L2 gene, the amount of TCF7L2 protein in the β-cells increases, which leads to a violation of insulin secretion, incretion effects and an increased glucose production rate in the liver [22].

In the islets of the pancreas of a patient with type 2 diabetes, expression of TCF7L2 is increased fivefold (especially in homozygotes), and over expression of this gene reduces glucose-stimulated insulin production. These data were confirmed by several subsequent studies, which led to the conclusion about the possible etiology of type 2 diabetes. The debut of the disease occurs due to a decrease in insulin secretion by β-cells, possibly due to the impaired action of in cretins, which leads to a change in the insulin response to food intake [9, 15, 25].

In other studies of this gene, it was determined that alternative splicing of the TCF7L2 gene leads to the formation of multiple isoforms in different tissues of the body, which, in addition to impaired insulin secretion, causes a decrease in insulin sensitivity by target tissues, such as adipose tissue [9]. Recent studies also showed the relationship of the TCF7L2 gene not only with type 2 diabetes, but also with cancer [13, 14]. When searching for candidate genes of any pathology, as mentioned above, they are guided by knowledge of the etiology and pathogenesis of the disease, clinical manifestations, development and progression of complications. Scientists focused on known pathways of glucose metabolism, insulin secretion and insulin receptors, as well as lipid metabolism [9] to determine the candidate genes for type 2 diabetes. However, in practice it turned out that not all of the alleged genes responsible for the development of type 2 diabetes, confirmed their participation in the research. In this section, some candidate genes will be considered, the connection of which with type 2 diabetes was substantiated in the conducted studies.

It is known that it is known for its development of type 2 diabetes. It makes it possible to increase the sensitivity of muscle tissue and adipose tissue to insulin, that is, to reduce insulin resistance. The effect of thiazolidinedione is mediated by their potent agonist affect with gamma receptors activated by the peroxisome proliferator (PPARG). It is included in the group of transcription factors. It is the result of exposure to the cell nucleic receptors and the lipids [1]. The PPARG has been found to be a substitute for proline by 20%. Nevertheless, it is not ubiquitous that prevails [9]. HNF1A, HNF1B and HNF4A genes, which cause monogenic diabetes, i.e., MODY. It is noted that the population increases the incidence of type 2 diabetes. However, the role of the HNF1A, HNF1B and HNF4A genes is quite small in the case of polygenic diabetes. For example, the glucokinase gene can be diagnosed, for example, the glucokinase gene. It is not possible to make a diagnosis of diabetes. the correct diagnosis. In other studies, the role of genes was shown. Insulin receptor (IRS1 and IRS2), which is a signal transduction. It is noted that it is associated with a decrease in insulin resistance.

In addition, some connection with type 2 diabetes was found in the KCNJ11 gene, an ATP-sensitive potassium channel involved in the regulation of insulin secretion by pancreatic β-cells, and the WFS-1 gene encoding a defective protein that occurs in Wolfram syndrome, which is characterized by juvenile diabetes, optic nerve atrophy and deafness [2]. Unfortunately, the value of both the listed and many other candidate genes cannot be overestimated, as it has not yet been possible to reliably prove their confident connection with the development of type 2 diabetes.

Diabetic nephropathy (DN) is one of the most serious complications of diabetes, the frequency of which progressively increases with the duration of the disease. However, a paradox was also noted regarding DNF, in which patients with no clinical and metabolic compensation for diabetes with additional risk factors for DNF, such as hypertension, hypercholesterolemia and hypertriglyceridemia, kidney damage is minimal or significantly delayed. Other DNFs can quickly form even under conditions of careful metabolic and hemodynamic control. These dissociations indicate the likelihood of a genetic explanation for the development of nephropathy [7].

When studying the genetic background of DNF, the most important pathogenesis pathways of this complication were taken into account, including increasing the activity of growth factors and cytokines (transforming growth factor in (TGF-c)), growth hormone (GH), insulin-like growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF). The activation of various isoforms of protein kinase C, enhancement of the effects of renin, angiotensin, endothelin, and bradykinin, the formation of reactive oxygen species, activation of aldose reductase, and increased glucose metabolism by pathological pathways have also been studied [21].

The study of candidate genes associated with the listed pathogenesis pathways in different populations resulted in ambiguous and sometimes contradictory data. One of the most studied candidate genes for DNF can rightly be considered the ACE gene involved in the renin-angiotensin-aldosterone regulatory system. The ACE gene exists in two versions: one with normal sizes - option I, the other, denoted as option D, with a missing small segment, which determines the so-calledinsertional deletion (I/D, insertion/deletion -

insertion/absence of insertion) polymorphism. There is a relationship between the genotype of the ACE gene and the concentration of tissue agiotensin-converting enzyme (ACE). The highest enzyme activity is detected in D/D homozygotes, the lowest in homozygotes I/I, and intermediate in heterozygotes I/D [7].

The contribution of the polymorphism of the ACE I/D gene can be estimated using the latest major meta-analysis based on 47 studies published between 1994 and 2004 inclusive. For instance, the I/I polymorphism of the ACE gene has nephroprotective properties in Asian patients with type 2 diabetes, while in Caucasian patients with type 2 and type 1, this connection is not confirmed. It was also shown that with I/D polymorphism of the ACE gene there is a good response to treatment with ACE inhibitors, however, the nephroprotective effect is more pronounced with the I / I genotype (20, 23, 28). Some studies have shown that the response to treatment with ACE inhibitors and the nephroprotective effect is better pronouncedin homozygotes for genotype I/I [20, 28].

There is evidence to support the concept of genetic susceptibility to nephropathy in patients with type 2 diabetes. First, diabetologists have long recognized that a number of patients develop nephropathy despite apparently good glycemic control, and vice versa, some patients with chronic hyperglycemia, reflecting indistinguishable control diabetes seems to be spared from this complication. Secondly, if the development of nephropathy was directly related to the total glycemic load, the prevalence is expected to increase steadily with increasing duration of diabetes. However, the peak frequency of nephropathy occurs between 10 and 20 years after the onset of diabetes, with a decrease in the frequency after that, indeed, only 25–40% of patients with type 2 diabetes will develop nephropathy [5–8]. Third, several studies have demonstrated familial clustering of nephropathy [9, 10]; if two or more siblings have diabetes, the risk of developing a second nephropathy for the second sister is about three times greater if the first sister has diabetic kidney disease. In addition, diabetic offspring of parents with hypertension or cardiovascular disease often develops nephropathy, affecting the fact that genes that confer the risk of hypertension. The general population predisposes to kidney disease in patients with diabetes [11].

The discovery of genetic variants that underlie susceptibility to nephropathy can provide important information on this condition. Firstly, it would allow identifying patients with a risk of nephropathy soon after diagnosing diabetes, and not much later, when persistent microacumuria develops, by that time there is already an egological evidence of kidney damage. This has facilitated fast-targeted therapeutic interventions aimed at primary prevention rather than secondary treatment of nephropathy. Secondly, and, perhaps more importantly, if susceptibility options are located in genes that have not previously participated in diabetic nephropathy, this may lead to an improved understanding of its pathophysiology and the development of new treatments. In addition, it is possible that variants of the genetic susceptibility may be specific for type 2 diabetic nephropathy, but they may be common for type 2 diabetic nephropathy or indeed other forms of kidney disease.

Identifying variants of genes that predispose to diabetic nephropathy is a difficult task. Unlike monogenic disorders, in which a relatively rare mutation in one gene usually gives a very high risk of developing the disease, susceptibility to diabetic nephropathy will most likely be determined by a large number of relatively common alleles of variants, each of which individually gives a modest increase in relative at risk. Thus, the risk of developing nephropathy is the summation of the effects of alleles present at each susceptibility locus, interacting with each other and with environmental factors, such as long-term glycemic and blood pressure control. The most common forms of human gene changes are single nucleotide polymorphisms (SNP) are single base substitutions, insertions or deletions that occur with a frequency of at least 1% in a given population. It is estimated that more than 10 million SNPs in the human genome occur at an approximate frequency of one out of every 300 base pairs [12]. Additional genomes arise through inherited duplicated or deletions of short chromosome segments; each person, therefore, may be less or more than the standard two parental alleles for each gene, signs like a change in the number of the instance [13]. In addition, genetic and environmental factors also contribute to variations in epigenetic phenomena, such as DNA methylation, which can affect gene expression and the risk of developing diseases [14].

Type 2 diabetes mellitus is complicated with DN and then leads to chronic renal failure (CRF) accompanying chronic kidney disease (CKD). In consequence, it leads to hemodialysis.

CKD is defined as renal damage, which is characterized by structural or functional kidney abnormalities or glomerular filtration rate (GFR) $<$60 ml/min/1.73 m, with or without renal injury for at least three months, without taking into account its causes [2].DN is characterized by a set of diabetic pathophysiological changes that begin with glomerularhyperfiltration and hypertrophy of the kidneys, and then progress in proteinuria and contraction of GFR. Based on the level of urine albumin excretion in a didactic person. DN has two phases: initial nephropathy or microalbuminuria phase with urine albumin (GAE) excretion in the range of 20 to 199 μg/min (or 30-300 mg/24 h); and, clinical nephropathy or proteinuria phase with GAE$>$199 μg/min ($>$300 mg/24 h) or proteinuria $\geq$500 mg/24 h. Microalbuminuria is considered as arisk

factor for DN progression [3]. In approximately 20-30% of patients with types 1 and 2 DM develops DN; however, a smaller proportion of patients with type 2 diabetes will progress to the end stage of renal disease (ESRD). Because of its high prevalence, most patients requiring dialysis are type 2 diabetes. DN is the most common cause of ESRD in a number of countries [4, 5], but not all diabetic individuals will develop this complication. Those who do not develop NAM in the first 15 years after the onset of the disease appear to be genetically protected [6]. Many environmental factors have been identified as contributing to the development of NAM, while the role of other people remains to be clearly understood [7]. Known factors such as hyperglycemia, arterial hypertension and/or dyslipidemia play a role in the development of DN only in genetically predisposed persons. The hospitalization rates for all causes are three times higher in patients with CKD than in those without disease [8]. According to Pagano et al. [9], patients with type 2 diabetes with DN and peripheral arterial disease are 1,2 – 1,3 times more likely to be hospitalized [9]. In addition, ESRD is associated with an increase in mortality, mainly due to cardiovascular reasons [10]. Reduced renal function is itself a high mortality rate. Other associated risk factors such as hypertension and autonomic neuropathy may contribute to cardiovascular diseases [10]. Even patients with DN, initially characterized by microalbuminuria, already have an increased risk of developing cardiovascular diseases and higher mortality [11]. In accordance with accumulated evidence, the risk of DN and cardiovascular diseases begin when GAE values are still within normal limits [12]. Some authors consider albuminuria to be the main risk factor for cardiovascular events, and not only the simplest marker for DN of progress [13], since some patients develop fatal cardiovascular events even before the appearance of reduced kidney function. In the metropolitan area of Porto Alegri, southern Brazil, 25% of new patients need dialysis because of diabetes, and they show high mortality during the first two years on dialysis [14]. So far, it has not been clearly established that some patients with diabetes will progress loss of kidney function and will require dialysis, while others will maintain normal kidney function. The study focused on the search for potential genetic changes associated with CKD and EPR. In fact, genetic evidence was found in the case of control and communication and more recently in research. These studies support the assumption that, on the set, the progression and severity of the DN may be partly associated with genetic factors [15]. Identification of genes associated with DN will allow one to recognize those who are at a high level of development of this complication. It will also allow a better understanding of the mechanisms and progress of the DM. Early and more aggressive treatment may provide high risk to the patients. Therefore, it is associated with high disease and mortality. Achieving pharmacogenetic studies can help treatment of choice by choosing renoprotective drugs according to individual hopl types [16]. This review discusses key information available in the literature that confirms the importance of genetic factors in DN. Also summarized are some of the results of our recent geo-institutional research.

The mode of genetic transmission of DN is still controversial. Theoretically, as with other diseases, this can occur in three different forms, which will lead to the development of DN [6, 17]. Monogenic form: mutations in the gene with a dominant role. Oligogenic form: mutations/polymorphisms of several genes would contribute to an independent and cumulative way of increasing susceptibility. Polygenic form: changes in many DNA loci and each of them will have a small and cumulative effect on DN development. Considering that DN is a multi factorial disease, the mode of transmission is likely to be polygenic, as well asgeosynthetic interaction with other environmental factors and clinical data such as duration of DM, arterial hypertension, dyslipidemia, smoking will lead to DN growth. Researches about family aggregation are not clearly studied for mode of transmission, but they provide evidence this is a polygenic complex disease [6, 17]. On the other hand, studies using segregation analysis [18, 19] suggest that familial aggregation of NAM is mainly due to the action of the main genetic locus. This effect will correspond to a monogenic or oligogenic form, where few genes have a greater impact on the phenotype. Since several genes may be involved in the development of the DN, and many of them have not yet been identified, one cannot be absolutely sure about the exact pattern of heritability in most cases.

Genes that give susceptibility to DNcan be searched in different ways. A widespread method is the approach of genes of candidates. The search for candidate genes includes the study of polymorphisms in one or more genes that are potentially involved in the pathogenesis of the disease. This approach is useful even when the effect of a gene on the progression of the disease is small [17]. Candidate genes are often analyzed in case-control studies, comparing the frequency of polymorphic/mutations in candidate genes among patients with and without disease. This is a suitable study for the study of complex genetic transmission, and it is especially useful in situations where genetic influence is relatively small, and disease-related alleles are common among the population [17]. However, this approach is very sensitive to stratification of the population, which can lead to false associations. In light of this, it was proposed that these studies include obtaining very small valuesof p and be based on reasonable a priori assumptions. This approach allowed us to describe many polymorphisms associated with DN; however, the results of the study were inconsistent.

One of the most studied changes is the insertion / deletion of the angiotensin-converting enzyme [ACE] gene. Meta-analysis showed that the D allele is associated with a high risk of DN [20]. Another approach used to analyze candidate genes is a non-equilibrium transfer test (TDT). This test is not affected by population stratification, but information is required about individuals studied and their parents and only parents of heterozygotes are informative. The frequency of transmission of the risk allele is comparable to the expected 50%. Its main limitation is access to a person and his parents, especially for DN type 2, which has a late start in life. In the case, demonstrated that the gene ectoenzymenucleotidepyrophosphatephosphodiestera (ENPP1) is associated with the early development of ERSD in patients with DN [21], and using the TDT approach, we confirmed that this association was not caused by aratification [24]. Recently, candidate genes are being tested in prospective studies. This study design is less susceptible to survival than research related to disease control, but they are more expensive and time consuming. Alternatively, the authors study cohorts that have been for a long period of time [23]. The limitation of these studies is that they are not specifically designed for the genetic effect of a particular gene. The use of microchips made it possible to quickly and accurately analyze a large number of candidate genes and execute GWS based on single nucleotide polymorphisms (SNPs). GWS can identify chromosomal regions that contain genes that are potentially involved in the genesis of the disease being studied. Panels of microsatellite markers or SNP at intervals of ~10 centimorgans (cM) in the entire genome are genotyped in several generations of families of patients with DN, or not having DN affected. Markers that are most often found in family members with DN indicate the location of the functional variant associated with the disease, and in a non-equilibrium state of adhesion with the marker. Given the difficulty of finding a large family with several members affected by DN, an alternative approach is to compare the observed and expected frequency of markers in pairs of diabetic siblings and inconsistency for DN. The main advantage over the candidate approach is that this approach can detect chromosomal regions containing genes that were previously not known to be involved in the pathogenic presentation of NAM. However, it has the disadvantage only to remove determinative genes that have a moderate or large effect [24]. Using GWS, we identified three polymorphisms found on chromosomes 9q and 11p associated with DN in two different populations of patients with type 2 diabetes [25]. Studies of familial aggregation showed that some families are susceptible to DN [26-28]. Studies on siblings with type 1 or type 2 showed that DN of siblings is associated with an approximately 3-4-fold increase in the risk of DN with another brother [29, 30]. There appears to be genetic inheritance that contributes to the development of CKD. Forsblom et al. [31] showed that heritability (h2) in the UAE is about 30% when analyzing non-diabetic type 2 diabetic children in children [31]. This conclusion was confirmed by another study, in which it was found that after adjustments such as gender, age, obesity and DN, approximately 30% of the variability in the speed of albumin and creatinine is due to genetic factors [32]. The magnitude of the family association cannot be attributed only to exposure to similar risk factors, with the result that there is a genetic component [33]. Although proteinuria and loss of kidney function often occur simultaneously, there is evidence of different geo-information predispositions for each condition [15]. This may explain why some patients may have resistant protein-disease without the progression of loss of kidney function [34] and other patients have renal function without proteinuria or microalbuminuria [15, 35]. In genetic association studies, it is very important to defineclearly the phenotype of interest. Most studies of heritability use albuminuria or proteinuria as a DN marker. In fact, the loss of kidney function measured by GFR is strongly associated with an increase in OAE. However, it is important to note that a significant proportion of patients with DN develop kidney function loss, but they support albuminuria [35–37] and, conversely, some patients with clinical proteinuria maintain stable GFR for many years [38]. The abbreviation of OAE and GFR is genetically determined, but apparently independently [15]. Langefeld et al. [39] evaluated 310 families, including 662 patients with DN 2 type and found h2 0.35 for OAE and 0.69 for GFR [39]. These data were similar to those described in other studies, h2 creatinine concentration 0.63 among mono and dizygotic twins [35].

One approach to the identification of genes associated with DN is the study of candidate genes. There are many studies of candidate genes for DN, but the results are incompatible. The choice of gene to be studied depends on knowledge of its actions in DNA pathophysiology, such as those related to blood pressure control, the severity of proteinuria, or insulin resistance [21]. Below we present our experience with this approach. Patients with type 2 with Microalbuminuria have a high level of circulating fatty acids [50] in the serum compared with norminobuminuric patients. The intestinal absorption of long chain fatty acids is controlled by fatty acid binding protein 2 (FABP2). Thus, changes in the gene that codifies FABP2 may be candidates indicating a predisposition for DN. A54T polymorphism (rs1799883) in FABP2 is associated with an altered protein conformation, which leads to a greater affinity of FABP2 protein for intestinal fatty acids with a subsequent increase in serum. We genotyped this polymorphism in 1042 Brazilian patients with type 2 DN. The T-allele link was found at different stages of DN [28]. This

association was reproduced in an independent sample of 483 whites. American test subjects with type 2 diabetes [28]. Several studies have analyzed insertion / deletion (I/D) of polymorphism in the ACE gene, but the results of its association with DN in patients with type 2 DN were inconsistent, possibly due to ethnic differences in the populations under study [20]. In addition, several studies have used a longer duration of DN as a critical inclusion interval, which may predispose to survival bias, since possible genes associated with DN can also be associated with increased mortality. Therefore, we chose to investigate the potential link between the I/D polymorphism in the ACE gene and the development of DN in 982 Brazilian patients with type 2 DN, taking into account the duration of their disease. In patients 10 years or less from a disease with the D allele (DD/ID), the odds ratio (OR) was 2.66 (95% CI 1.12-6.58, p = 0.015) for initial DN and 3, 19 (95% CI 1.18–9.30, p = 0.012) for open dm. On the other hand, in patients with a longer duration of the disease, an increased risk for DN was associated with allele D [35]. Candidate genes for insulin resistance can also be considered candidates for the Duma, since insulin resistance is a common characteristic of patients with type 1 and type 2, which represent an increased OAE [21, 32]. Polymorphism in the ENPP1 gene, previously known as PC-1 was found to be associated with insulin resistance [33]. This association was confirmed using TDT, which showed that this association was not caused by population stratification [21]. GLUT1 gene polymorphisms associated with DNs were also considered. GLUT1 is a carrier of glucose in the kidney, and this has been associated with early kidney changes leading to proteinuria. We studied 230 patients (patients with DN 2, disease duration of at least 15 years and normoalbuminuria) and 262 cases (151 patients with persistent proteinuria and 111 with ESRD). Homozygotes for the Xbal (-) allele were associated with a discrete increased risk for DN when compared to other genotypes combined [OR 1.83 (95% CI 1.01-3.33)]. A significant difference in the distribution of genotypes among cases and controls was observed for the enhancer-2 SNP1 (p = 0.036). There was an excess of the AA genotype among cases (10.7%) compared with the control group (4.8%). These homozygous individuals are at risk for DN compared with the AG and GG genotypes mixed [OR 2.38 (95% CI 1, 16-4.90)] [23]. Other studies analyzed different genes and did not find a connection with the DN (Table 1). One of these studies showed that when patients stratified smoking, the T allele (p22phox C242T polymorphism; rs4673) was more common in ESRD smokers or resistant proteinuria than in patients with normal albumin-recipient (43% vs 32%, p=0.045). Repeated logistic regression analysis confirmed that CT and TT genotypes were independently associated with a greater risk of open DN among smokers (OR = 6.76; 95% CI 1.83-25.02) [36]. Our experience with candidate genes has allowed us to identify some genes that may be associated with the development and seriousness of DN.

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Global Journal of Medical Research: F
Diseases
Volume 19 Issue 1 Version 1.0 Year 2019
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Combined Positron-Emission and Computed Tomography in the Study of the Kidneys Energy Metabolism

By Berdichevskyy B. A. & Berdichevskiy V. B.

Relevance- Biochemical reactions that provide the process of urine secretion and excretion are well studied, and they are based on the energy-dependent transmembrane movement of molecules on both sides of the nephron. This unique machine is designed in such a way that not only the physiological processes of its activity, but also pathological destructive reactions require the use of biological energy carriers. So a fast source of energy is a glucose molecule built into the membrane ATP-ASE, the long-term carrier of energy potential are lipids, or rather membrane phospholipids containing a molecule of choline. These energy "swings" are the essence of the entropy of living matter [1-6].

GJMR-F Classification: *NLMC Code: WN 206*

Strictly as per the compliance and regulations of:

Combined Positron-Emission and Computed Tomography in the Study of the Kidneys Energy Metabolism

Berdichevskyy B. A. [α] & Berdichevskiy V. B. [σ]

Relevance- **Biochemical reactions that provide the process of urine secretion and excretion are well studied, and they are based on the energy-dependent transmembrane movement of molecules on both sides of the nephron. This unique machine is designed in such a way that not only the physiological processes of its activity, but also pathological destructive reactions require the use of biological energy carriers. So a fast source of energy is a glucose molecule built into the membrane ATP-ASE, the long-term carrier of energy potential are lipids, or rather membrane phospholipids containing a molecule of choline. These energy "swings" are the essence of the entropy of living matter [1-6].**

I. The Purpose of Research

The purpose of research was to study the possibility of use of positron-emission and computed tomography (PET/CT) with the isotope (18F-FDG) of glucose and 11c-choline in the study of the energy balance of the kidney parenchyma in the process of physiological urine formation.

II. Materials and Methods

To achieve this goal, a retrospective analysis of 60 PET/CT findings of the entire human body was conducted. In 30 cases with the isotope (18F-FDG) of glucose and in 30 cases with the isotope 11c-choline in patients with melanoma examined for the possible presence of metastases. These were young people aged 25-35 years old without any concomitant nephrological pathologies. The combined positron emission and computer tomography were performed according to the standard method on the PET device | CT (Siemens Biograph) production of Germany. Any functional changes in the kidney parenchyma in the regions of increased 18F-FDG glucose or 11c methionine metabolism in the process of physiological urinary formation were studied. The zones of interest were analysed by a semi-quantitative measure and the bar-line was mapped. In these zones, the value of the standard capture level (Suv max) was calculated. The calculation was performed automatically by the program complex. As the normal range, in the digital value, the indicators were in the range of 3.5-6.5 conditional units.

III. The Results of the Study

In the process of retrospective analysis of the results of PET/CT kidney parenchyma scans, we were interested in the metabolism of 18F-FDG glucose, as a fast source of energy, providing glomerular filtration and tubular reabsorption. The results are presented on the Tomogram 1.

From the presented data it is visible, that glucose metabolism has special characteristics independent from morphological localization in the nephron region (renal medulla or cortex) and, apparently, reflects the phase process of urinary formation in the mode of real time.

The results of the analysis of long-term carrier metabolism of energy potential in the composition of membrane phospholipids containing the molecule of marked 11c-choline and providing physiological fluidity of the kidney membrane filter are presented on Tomogram 2.

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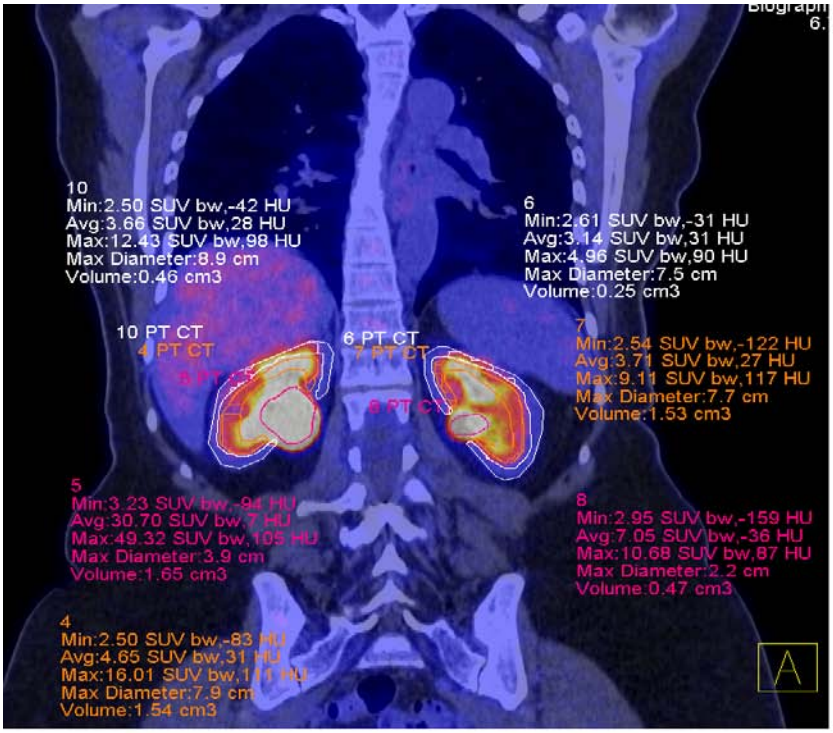
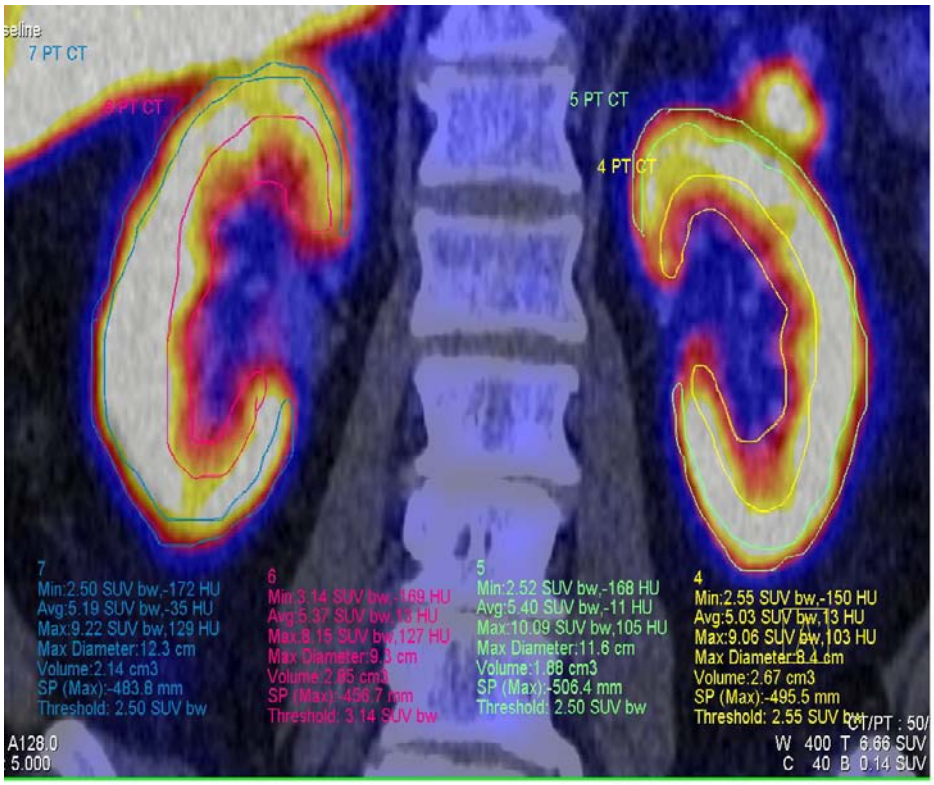


Tomogram 1: Kidney PET/CT with 18F-FDG glucose



Tomogram 2: Kidney PET/CT with 11c-choline

The presented Tomograms visualize clear regional distribution of the intensity of fixation of choline indicating its deficit, first of all at the level of the medulla layer of the kidney, and then the cortex. We can assume that the medulla layer of the kidney in the long-term mode is more energy-dependent and it requires special research. The mathematical analysis of the presented data (SUV max) can be one of the confirmations of the stated assumptions.

IV. Conclusions

As a result of the conducted research the possibility of investigation of the energy metabolism of kidneys by the method of PET/CT with isotopes 18F-FDG and 11c-choline in the process of physiological urinary formation is established.

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Global Journal of Medical Research: F
Diseases
Volume 19 Issue 1 Version 1.0 Year 2019
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

The Role of new Prognostic Markers and Comorbidities on the Outcome of Patients with Chronic Lymphocytic Leukemia in a Malaysian Referral Centre

By Dr. Lee Bee Sun, Dr. Tan Sen Mui, Ms. Phan Chin Lee, Prof. Dr. Cheong Soon Keong & Dato Dr. Chang Kian Meng
Universiti Tunku Abdul Rahman UTAR

Introduction- Chronic lymphocytic leukemia (CLL) is a clonal lymphoid neoplasm characterized by proliferation and accumulation of neoplastic B lymphocytes in the blood, bone marrow, lymph nodes, and/or spleen. In Western countries, CLL is the most common leukemia in adults, accounting for 5% to 11% of lymphoproliferative disorders (LPD). The incidence rate is between 2 to 6 cases per 100 000 with an increasing trend as people get older.[1] The incidence of CLL is lower in Asian subjects, including Malaysians. In Asian countries, CLL accounts for only 1% to 3% of LPD in most series.[2] Asian CLL has been reported to have different biological characteristics with a more aggressive clinical course and treatment outcomes when compared with those of Western CLL. The reasons for these differences in incidences and clinical behaviour between geographic regions are unclear but are of considerable interest. Data on CLL in Asian countries including Malaysia is also very limited because of the disease rarity.

GJMR-F Classification: NLMC Code: QZ 350

The Role of new Prognostic Markers and Comorbidities on the Outcome of Patients with Chronic Lymphocytic Leukemia in a Malaysian Referral Centre

Dr. Lee Bee Sun [α], Dr. Tan Sen Mui [σ], Ms. Phan Chin Lee [ρ], Prof. Dr. Cheong Soon Keong [Ω] & Dato Dr. Chang Kian Meng [¥]

I. Introduction

Chronic lymphocytic leukemia (CLL) is a clonal lymphoid neoplasm characterized by proliferation and accumulation of neoplastic B lymphocytes in the blood, bone marrow, lymph nodes, and/or spleen. In Western countries, CLL is the most common leukemia in adults, accounting for 5% to 11% of lymphoproliferative disorders (LPD). The incidence rate is between 2 to 6 cases per 100 000 with an increasing trend as people get older.[1] The incidence of CLL is lower in Asian subjects, including Malaysians. In Asian countries, CLL accounts for only 1% to 3% of LPD in most series.[2] Asian CLL has been reported to have different biological characteristics with a more aggressive clinical course and treatment outcomes when compared with those of Western CLL. The reasons for these differences in incidences and clinical behaviour between geographic regions are unclear but are of considerable interest. Data on CLL in Asian countries including Malaysia is also very limited because of the disease rarity.

Chronic lymphocytic leukemia has a heterogenous clinical course, ranging from relatively indolent to aggressive. At diagnosis, staging of disease can be made based on the Rai clinical staging system[3] and the Binet staging system[4]. However both staging systems have limited value in determining the clinical course of the disease in individual cases and in the identification of progressive CLL, especially during the early stages of the disease. Over the past several years, new markers with significant prognostic values have been identified. Unlike the "old" staging systems, the "newer" markers such as immunoglobulin heavy-chain variable region (IgVH) mutation status, fluorescence in-situ hybridization (FISH) cytogenetics, and CD38 and zeta-associated protein (ZAP)-70 expressions may reveal an underlying biological connection with the disease.[5] Furthermore various investigators have reported the importance of these prognostic markers not only useful to address disease progression and overall survival, but also to predict response to therapy.[6]

A set of specific chromosomal abnormalities has been reported to have predictive value for disease course and outcome. Listed in order of increasing disease severity, these include 13q14 deletion (13q-), trisomy 12, 11q22-23 deletion (11q-), and 17p deletion (17p-).[5] In the late 1990s, a novel technique looking at chromosomal abnormalities was developed which was called inter phase FISH, and this method was well suited for use in CLL, given its low mitotic rate.[7] With FISH, the number of chromosomal abnormalities seen in CLL increased from 51% to 82%.[7] At present FISH has become the standard method to detect chromosomal abnormalities in the clinical care of CLL patients. Detection of these cytogenetic abnormalities has apparent prognostic value and may influence therapeutic decisions. Additional genetic defects may be acquired during the course of the disease and therefore, the repetition of FISH analyses seems justified before subsequent second and third-line treatment.

Besides, expression of CD38 on and ZAP-70 in CLL cells has proven valuable in predicting outcome in CLL. CD38 expression is a measure of cell division and a reflection of growth in vivo. The percentage of cells within a CLL clone that display CD38 is an indicator of the potential and actual degree of cellular activation of the clone: those with higher numbers (than a defined percentage) are more responsive to activation signals or are activated and are therefore more often more aggressive.[5] CD38 expression can be evaluated by flow cytometry and its positivity is usually associated with a more virulent and progressive disease. Besides CD38 expression, intracellular expression of the ZAP-70 protein above a certain threshold of cells measured by

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immune fluorescence and flow cytometry has proven to be an important indicator of time-to-treatment and survival in CLL.[8] These "newer" predictive prognostic markers on CLL patients' outcomes have never been reported in Malaysia.

As CLL is a disease of the elderly with a median age of 67-72 years at diagnosis,1 the majority of patients with CLL commonly present with multiple comorbidities at presentation or when treatment is indicated. Recently, comorbidity was identified as an adverse prognostic factor in patients with untreated or treated CLL.[9] Several recent randomized trials deliberately focused on patients with comorbidities, using the cumulative illness rating scale (CIRS) as a semi-quantitative tool. The CIRS determines the burden of medical illness while taking into account the severity of each condition. However, the impact of comorbidities on CLL treatment outcomes and survival remains understudied in Malaysia. Thus, in this analysis, we aim to evaluate this impact as part of our objectives.

Although the incidence of CLL in Malaysia is lower than that in Western countries, a progressively increasing trend has been observed in recent years. No studies in Malaysia have so far reported on the relationship of these new prognostic markers and comorbidities with the outcome of CLL patients. The aim of this study is to analyze the clinical characteristics of patients with CLL in a Malaysian Hospital besides determining the relationship of cytogenetic abnormalities and CD38 expression on disease clinical course, and the interaction between comorbidity and treatment outcome. The findings of this study may help us improve the care, counseling and treatment strategy of CLL patients in Malaysia.

II. Materials and Methods

This observational study was carried out at the Hematology Department of Hospital Ampang, the national hematology referral centre in Malaysia from 1st January 2007 through 31st December 2016. The study enrolled 71 confirmed CLL patients with minimum one-year follow-up duration. The diagnosis of CLL was made according to the International Workshop of CLL (IWCLL) updated in 2008.10 Patients' data were retrospectively retrieved from the electronic hospital informative system. These include demographics, initial presenting features, laboratory results such as FISH cytogenetic profile and CD38 expression by flow cytometry, and first line chemotherapy administered. Besides, response to treatment and status of remission during follow-up period were also analyzed.

For comorbidity assessment, we captured the number of medical conditions present at baseline. Further quantification of the comorbidity burden was done using the CIRS score. Health problems resulting from the CLL itself were not recorded as comorbidity. The impact of high burden of medical illness, defined as CIRS ≥4 in this study was assessed and compared with those with CIRS 0 to 3.

The outcomes of disease were first investigated by using Kaplan-Meier (KM) product limit method and the log-rank test in accordance to sex, race, Binet staging, chromosomal abnormalities, CD38 expression, induction treatments and comorbidities burden. Two outcomes were assessed: Overall survival (OS) and progression free survival (PFS). Differences in OS and PFS with p-value less than 0.05 are considered statistically significant. The study was registered under the National Medical Research Register (NMRR), Malaysia. It was approved by the Medical Research & Ethics Committee (MREC), a centralized independent ethics committee for public hospitals in the country. The CIRS score (appendix I) was used to categorize and score each of the concomitant diseases.

III. Results

The survival analysis was performed in 71 CLL patients with minimum 12 months follow-up duration. The baseline demographic and characteristics of the patients are shown in Table 1. The median age at diagnosis was 64.0 year, ranging from 38.0 to 80.0 years. Male CLL patients accounted for 73.2% of the cohort. Malay patients accounted for 45.1% of the cohort, followed by 42.3% of Chinese patients, 11.3% of Indian patients and 1.4% of other ethnicity. According to the Binet staging system, majority of the CLL patients (45.1%) presented with Binet C, followed by Binet A (33.8%) and Binet B (21.1%).

The FISH cytogenetic profile was performed in 55 patients (77.5%). Chromosomal abnormalities in CLL were detected in 33 out of 55 patients (60.0%). Among the abnormalities, 13q- (27.3%), 17p- (14.5%), and tri12 (16.4%) had a known prognostic value and played an important role in CLL pathogenesis and disease progression, = determining the outcome and treatment strategies. The CD38 expression was documented in 61 out of 71 patients (85.9%), which included 14 (23.0%) CD38 positive and 47 (77.0%) CD38 negative patients.

Table 1: The Characteristics of CLL patients

No	Characteristics	N	(%)
1	Number of patients	71	
2	Age at diagnosis, years		
	Median (IQR)	64.0	(16.0)
	Mean (SD)	62.4	(10.2)
	Range, min – max	38.0 – 80.0	
3	Sex		
	Male	52	(73.2)
	Female	19	(26.8)
4	Race		
	Malay	32	(45.1)
	Chinese	30	(42.3)
	Indian	8	(11.3)
	Others	1	(1.4)
5	Disease classification		
	Binet A	24	(33.8)
	Binet B	15	(21.1)
	Binet C	32	(45.1)
6	FISH cytogenetics		
	Normal	22	(40.0)
	13q-	15	(27.3)
	17p-	8	(14.5)
	Trisomy 12	9	(16.4)
	Complex karyotype	1	(1.8)
	Not done	16	-
7	CD38 expression		
	CD38+	14	(23.0)
	CD38-	47	(77.0)
8	Induction treatment		
	Alkylating agent based	31	(43.7)
	Fludarabine based	7	(9.8)
	Ibrutinib	1	(1.4)
	No treatment	32	(45.1)
9	Disease progression		
	Yes	28	(39.4)
	No	43	(60.6)
10	Disease mortality		
	Death	25	(35.2)
	Alive	46	(64.8)

Characteristics of CLL patients are described by absolute count (n) and percentage (%) unless otherwise specified.

The patients' comorbidity burden is presented in Table 2. Among the patients population, 50.7% of them had at least one concurrent disease at diagnosis. Of the 24 patients presenting with ≥2 comorbidities, most had 2-3 co-existing diseases, while there were only 4 patients with >3 comorbidities. The two most common comorbidities were hypertension (32.9%) and diabetes (23.7%). Nineteen patients in the cohort had high burden of medical illness, defined as CIRS ≥4.

Table 2: The comorbidity burden of CLL patients

Characteristics	N (%)
Number of comorbidities	
0	35 (49.3)
1	12 (16.9)
≥2	24 (33.8)
CIRS score	
0 to 3	52 (73.2)
≥4	19 (26.8)

Decision to treat a CLL patient often relies on the clinical staging, the symptomatic presentation, and the disease activity. Patients in earlier stages (Rai 0-II, Binet A) are generally not treated but monitored with a "watch and wait" strategy. In our cohort, induction chemotherapy was started in 39 (54.9%) CLL patients with various regimes used. As first line therapy, chlorambucil and prednisolone (CP) regime was most commonly used at our setting due to its less toxicities and being a safer approach to our majority elderly patients especially those with multiple comorbidities. Other combinations of therapy used include cyclophosphamide, vincristine and prednisolone (CVP/COP) or cyclophosphamide, adriamycin, vincristine and prednisolone (CHOP) with combination of monoclonal anti-CD20 antibody rituximab in those patients with CD20 positivity, and fludarabine based regime such as fludarabine, cyclophosphamide and rituximab (FCR). Three of our patients were given obinutuzumab and chlorambucil combination and one patient with 17p- was given ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, both regimes made available under compassionate programmes.

Among the CLL patients, death was found in 25 out of 71 patients (35.2%); disease progression was found in 28 out of 71 patients (39.4%), with a minimum of 12 months follow-up duration. Survival analysis was performed for 55 patients (77.5%) who had FISH cytogenetic results. Survival curves were plotted among patients who had normal karyotypes, 13q-, 17p- and tri12. Inferior OS was found in patients with 17p- when compared to other chromosomal abnormalities, although result is not statistically significant ($p=0.0787$). According to the KM survival curve, the overall survival of patients with different karyotypes did not differ at the beginning of the disease until 50 months. At 50 months later, survival rate of patients with karyotype 17p- reduced greatly and all patients with karyotype 17p- died within 60 months. Patients with karyotype 17p- had the worse survival outcome with 62.5% mortality rate and a median OS of 48.033 months (95% CI: 5.260,58.257), as compared with other karyotype groups (Figure 1). Similar results were obtained for PFS, where inferior PFS was detected in patients with deletion of 17p ($p=0.0346$) when compared to other chromosomal abnormalities (Figure 2).

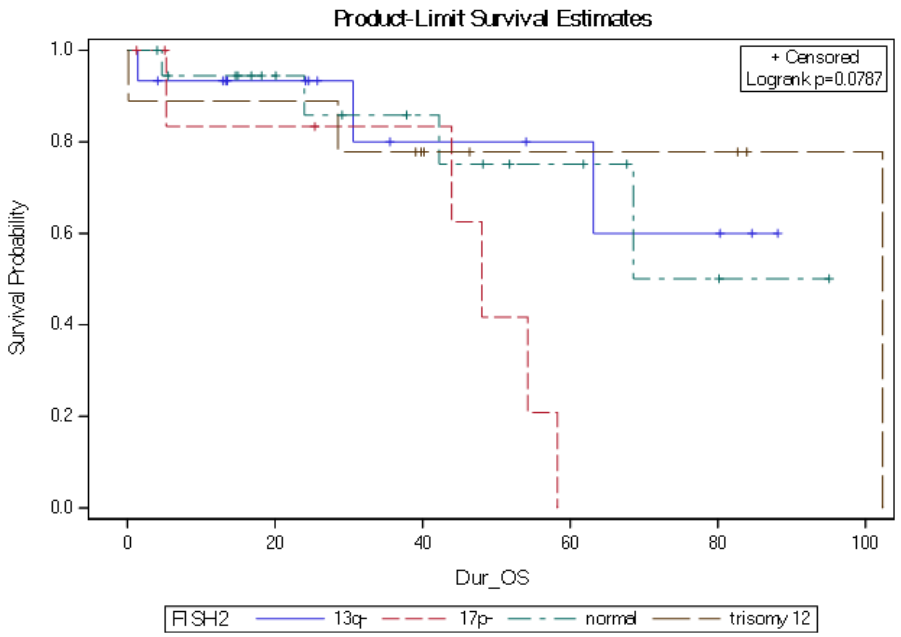

Figure 1: Overall survival of CLL patients according to FISH cytogenetics.

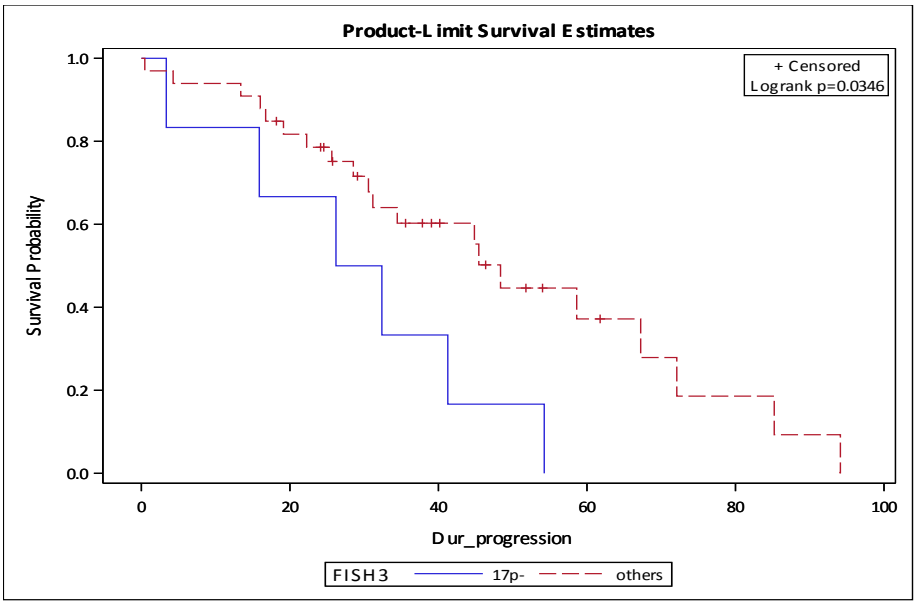

Figure 2: Progression free survival of CLL patients with 17p- compared to other chromosomal abnormalities.

From the analysis, OS of patients with different binet did not show statistically significant difference. However, patients with binet C were found to have highest mortality rate (43.8%) as compared with binet A (16.7%) and binet B (26.7%). The median OS of patients with binet C was 58.3 months (95% CI: 43.923, 102.312). The median overall survival of other binet groups cannot be estimated due to lack of events or insufficient follow-up duration (Figure 3). Patients with binet C also have inferior PFS compared to other groups, with median PFS of 32.38 (95% CI: 17.03, 48.36) months (Figure 4).

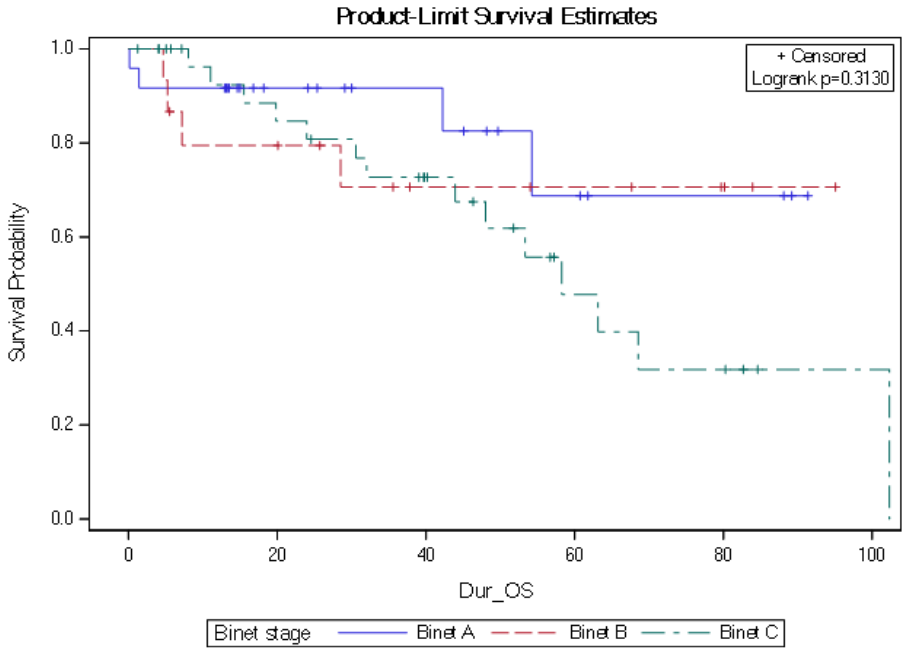

Figure 3: Overall survival of CLL patients according to binet staging.

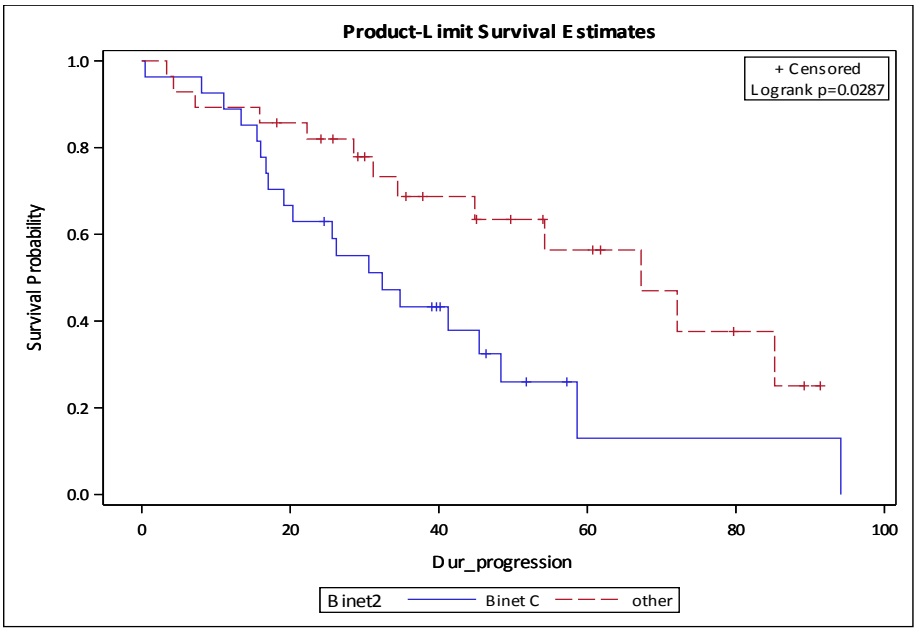

Figure 4: Progression free survival of CLL patients according to binet staging.

Overall survival of patients with CD38+ also did not show statistically significant difference from those with CD38- (p=0.1524). The median overall survival of patients with CD38+ was 53.326 months (95% CI: 28.537, 102.312) (Figure 5).

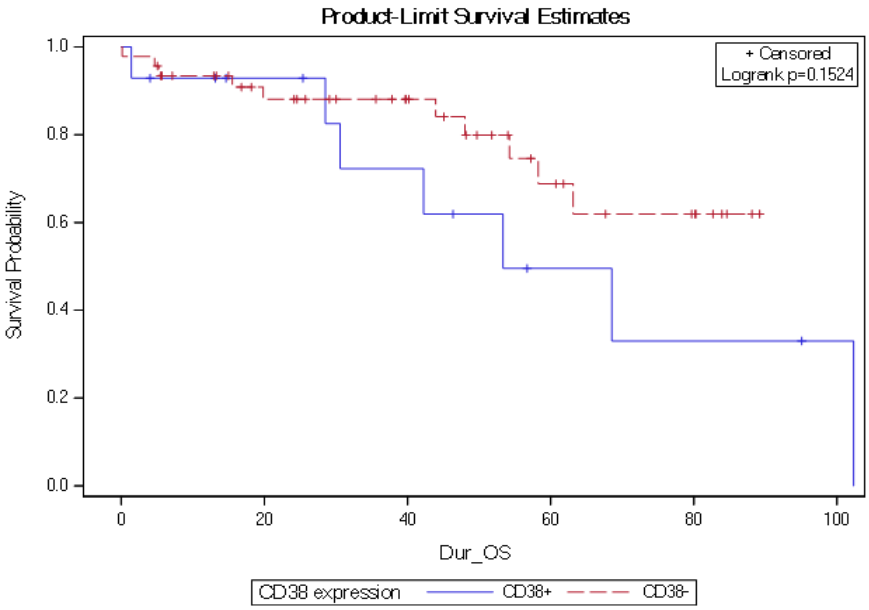

Figure 5: Overall survival of CLL patients according to CD38 positivity.

From the analysis, 39 patients who were treated for CLL presented inferior OS as compared with those who were not treated. The difference in OS is statistically significant (p=0.024) (Figure 6). Cox regression model (univariable) reveals that patients who were treated had 2.6 times higher hazards of death compared to those who were not treated (HR=2.653, p=0.042). Further analysis revealed that patients receiving fludarabine based induction protocol experienced inferior OS (median OS=48.0 months) as compared with those treated with alkylating based protocol (median OS=63.1 months). The difference in OS is statistically significant (p=0.032) (Figure 7). Cox regression model (univariable) reveals that patients receiving fludarabine based protocol had 3.15 times higher hazards of death compared to those treated with alkylating based protocol (HR=3.150, p=0.042).

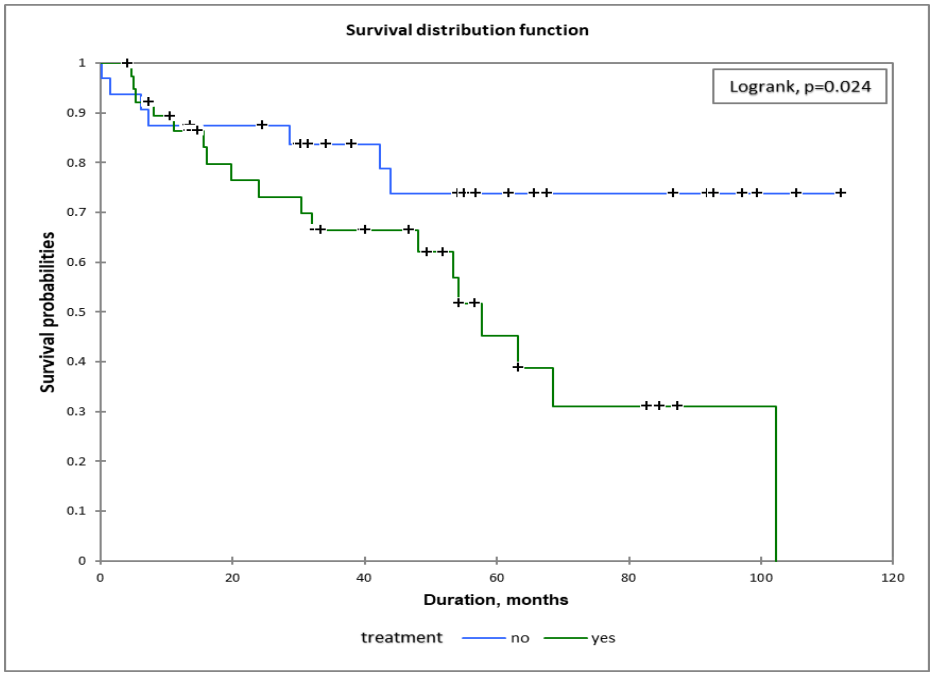

Figure 6: Overall survival of CLL patients according to treatment decision.

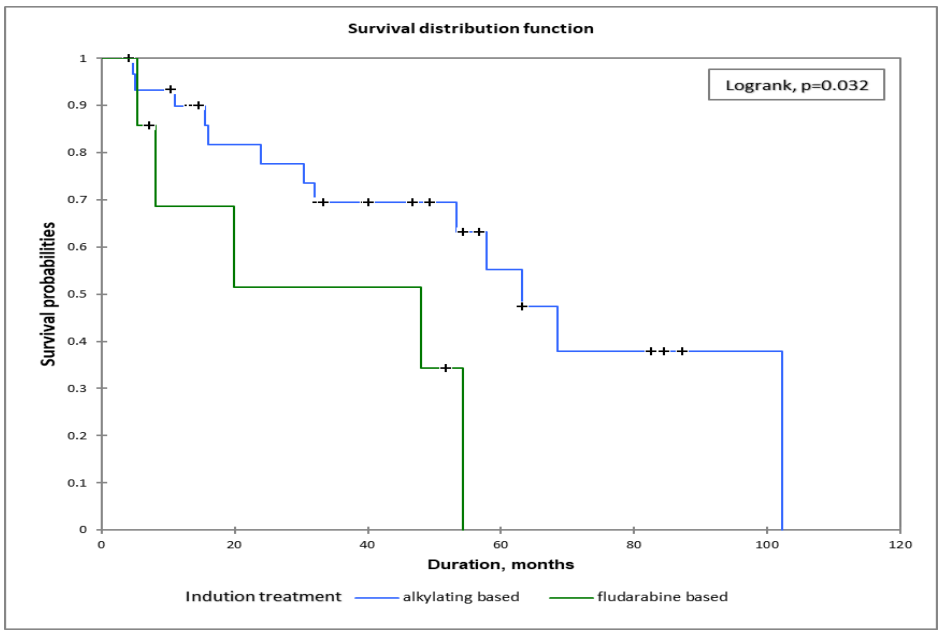

Figure 7: Overall survival of CLL patients according to induction treatment.

From our analysis, CIRS 0 to 3 has higher mortality when compared to CIRS ≥4 but survival analysis is not significant (Figures 8). This observation may be confounded by other co-variables with potential impact on OS such as age, treatment regimen, disease stage and disease risk.

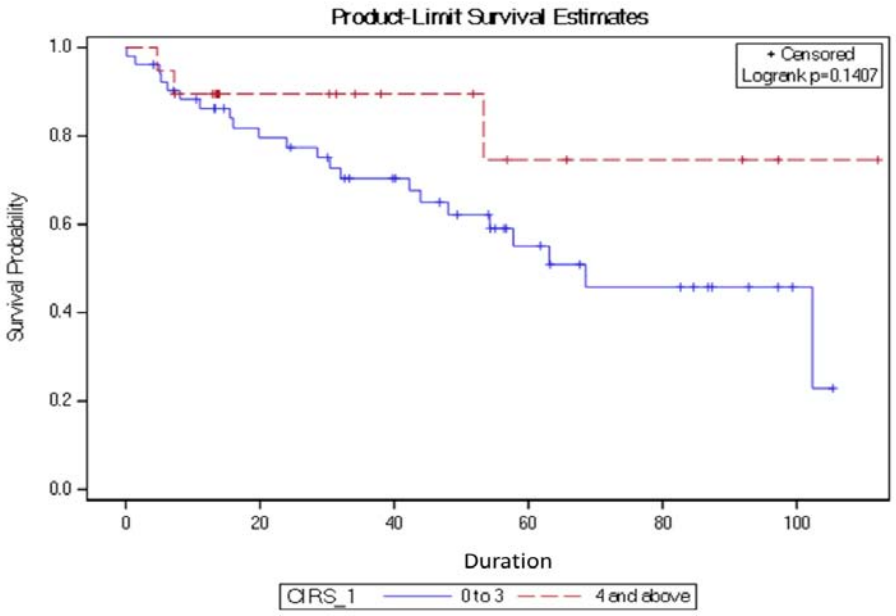

Figure 8: Overall survival of CLL patients by CIRS.

IV. Discussion

To our knowledge, this is the first study done looking at demographic data, clinical behavior as well as survival outcomes of CLL patients in Malaysia. The much lower incidence of CLL in Eastern countries, including Malaysia, is well known. Hence data on CLL in Asian countries is very limited. In Western populations, the median age at diagnosis lies between 67 and 72 years and more male than female patients (1.7:1) are affected.[11-13] In this study, the median age of our patients at diagnosis was 64 years with a male preponderance (2.7:1). The ethnic distribution for our CLL cohort was corresponding to our nation ethnic groups distribution, as majority were Malay patients.

In all cases, the diagnosis of CLL was established based on IWCLL by full blood counts, blood smears and peripheral blood for immunophenotyping. Further tests such as cytogenetic analysis by FISH and CD38 expression were analyzed as prognostic tools of the disease. In our cohort, a bone marrow was usually performed in cases with cytopenias (anaemia, thrombocytopenia) that may or may not be directly related to leukemia-cell infiltration of the marrow, or generally before initiating therapy when treatment was indicated. The diagnosis of CLL requires the presence of $\geq 5 \times 109$ B lymphocytes/L in the peripheral blood. The clonality of the circulating B-lymphocytes needs to be confirmed by flow cytometry, in which characteristically CLL cells co-express the T-cell antigen CD5 and B-cell surface antigens CD19, CD20, and CD23.

Once diagnosis of CLL is established, there are 2 widely accepted staging methods to stage the disease, the Rai clinical staging systems[3] and the Binet staging system.[4] Both systems provide not only a prognosis for a patient, but also identify when a patient is appropriate for therapy. To standardize the staging system, all the CLL patients in our cohort were staged according to the Binet system, which relied on the number of involved nodal areas and cytopenias to create a 3-group classification. Majority of our study population presented with higher risk disease, Binet stage C which is defined when there are presence of both cytopenias (hemoglobin $<$10g/dL and platelet $<$100x109/L) and any number of enlarged lymph nodes area. Binet stage C justifies treatment for all patients. We observed a poorer OS among our patients with Binet stage C with a median OS of 58.3 months, compared to other Binet stages. E. Montserrat[14] also demonstrated this observation in a study which showed patients with high-risk disease (Binet C; Rai stage III or IV) when compared to Binet stage A and B, have a worse median OS of 3-4 years.

Three of the four well-recognized cytogenetic abnormalities observed in CLL patients, including 13q-, trisomy 12, 11q- and 17p- are detected in our cohort except 11q-, with the highest frequency found in 13q- followed by trisomy 12 and 17p-. Patients with 17p- have been known to have an inferior prognosis and appear relatively resistant to standard chemotherapy regimes using alkylating drugs and/or purine analogs.[15-16] Our data demonstrated that patients with 17p- had inferior outcomes, both in OS and PFS. Based on our results, we concluded that both binet C and 17p- status may be able to predict disease progression among our patients. In addition, further analysis revealed that cohort with disease progression had inferior overall survival compared to those without disease progression (median OS=68.5 months, p=0.609).

Our analysis also showed that those who received treatment had inferior OS than those who were

not treated, with worse outcome in those who received fludarabinebased regime. Further analysis of the five deaths that occurred in the fludarabinebased group (71.4%) showed that three of them had 17p-, one had complex cytogenetic abnormalities and one presented w Binet stage C with no cytogenetic performed. Disease-related, instead of treatment-related toxicity was the major cause of death amongst the five patients. This observation showed that fludarabine-based regime was commonly selected as treatment choice in our cohort for majority of patients who presented with a higher risk disease, in which we have earlier demonstrated that this group had an inferior survival outcome.

CD38 expression on leukemic lymphocytes was found to correlate with IgVH mutations and predicted clinical outcome. Subsequent research confirmed the prognostic value of CD38 expression, but has questioned its ability to predict IgVH mutational status.17-18 However, the most appropriate threshold to define CD38- positivity is controversial. It has been suggested that rather than a fixed, arbitrarily predetermined cut-off level, CD38 should be evaluated by its modal expression in flow cytometry or by the antigen density as measured by the antibody-binding capacity.[19] Our study demonstrated that OS of patients with CD38 expression did not show statistically significant difference from those with CD38- ($p=0.1524$). Clearly, CD38 analysis and the most reliable method for using it to determine CLL prognosis requires standardization and additional, prospective studies.

Two retrospective studies recently reported on comorbidity as a prognostic factor in CLL.20-21 In subjects with cancers others than CLL, comorbidity is associated with shortened survival.[22] Assessment of comorbidities in CLL has not really been standardized. In our study, we assessed CIRS score at enrollment to determine the burden of comorbidities of our patients. Based on our analysis, however we demonstrated that CIRS 0 to 3 has higher mortality when compared to CIRS ≥ 4 but survival analysis is not significant ($p=0.1407$). In a retrospective study, this result may be confounded by other co-variables such as age, treatment choice and disease burden. This observation may also be compounded by the lower prevalence of comorbidities (50.7%) in our study compared to that in the general CLL population (90%).[23] The lower mortality observed in patients with CIRS ≥ 4 may be related to greater chance of dose attenuations of therapy which limits therapy-related toxicity and hence mortality.

V. Conclusion

In summary, although the numbers of patients diagnosed with CLL are still small in Malaysia compared to Western countries, the incidence of CLL is definitely gradually increasing. Hence, the increasing role of response predictors in prognostication cannot be overemphasized. Nonetheless, before a good prognostication system can be implemented, the methods to determine the prognostic parameters should be fully standardized and their prognostic value should be validated in large prospective clinical trials. Our analysis is, however limited by few factors that include missing data as well as short follow-up duration of 12 months. Future prospective studies are also needed to validate CIRS effect on overall survival so that we could optimize treatment strategies in this high-risk population, including in a setting of novel "targeted" therapies. We feel that researchers should take a more profound interest in the field of CLL, especially in the era of “precision medicine” whereby true predictive markers are highly desirable.

Acknowledgement

I acknowledge the important contributions of all the investigators who have participated in this study.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Global Journal of Medical Research: F
Diseases
Volume 19 Issue 1 Version 1.0 Year 2019
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Sleep Apnea Syndrome in Patients with Chronic Cerebral Venous Insufficiency on the Background of Chronic Obstructive Pulmonary Disease

By Janna Nazarova

Abstract- A clinical instrumental examination and polysomnographic examination were performed in 94 patients with chronic cerebral ischemia against the background of cerebral venous dysfunction with concomitant pathology - chronic obstructive pulmonary disease. 21 (22.3%) patients from the survey had clinical manifestations of obstructive sleep apnea/hypopnea sleep: mild - 3, moderate - 11, severe - 7. A significant correlation was shown between body mass index, the number of apnea episodes and the level of hemoglobin saturation with oxygen, symptoms of cerebral venous dysfunction. No correlation was found between forced expiratory volume indicator and for the 1st second. It should be assumed that in the pathogenesis of obstructive sleep apnea/hypopnea syndrome in chronic obstructive pulmonary disease, the degree of obesity and cerebralvenous dysfunction are more important, and not the severity of obstruction of the lower respiratory tract.

Keywords: *obstructive sleep apnea/hypopnea syndrome, polysomnography, cerebral venous dysfunction.*

GJMR-F Classification: *NLMC Code: WM 188*

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Keywords: obstructive sleep apnea/hypopnea syndrome, polysomnography, cerebral venous dysfunction.

I. Introduction

Cerebral venousdiscirculation (CVD) often occur with congestion in the system of the superior vena cava, right ventricular failure, impaired blood circulation in the pulmonary circulation. Moreover, in this category of patients, along with hemodynamic factors, in the development of this pathology, individual neuro-reflex mechanisms and primary pathological conditions leading to the development of dyscirculation in the venous system of the brain matter.

In patients with CVD on the background of chronic obstructive pulmonary disease (COPD), obstructive sleep apnea/hypopnea syndrome (OSA/HS) significantly aggravates the course of the underlying disease, increases hypoxemia, promotes the development of secondary erythrocytosis, pulmonary hypertension and the formation of chronic pulmonary heart with right ventricular failure [3, 9, 10].

The prevalence of OSA/HS among the entire population over 30 years is 5–7%. These figures are comparable with the prevalence of bronchial asthma. About 1–2% of this group of people suffer from severe forms of the syndrome. Among people older than 60 years, the frequency of OSA/HS increases significantly and is about 30% for men and about 20% for women. In persons older than 65 years, the incidence of this syndrome can reach 60% [1].

Combinations of COPD and OSA/HS - overlap syndrome - is a state of mutual aggravation. The prevalence of chiasm syndrome among persons with COPD is estimated at 2%, and among patients with OSA/HS - at 10%. In this regard, patients with COPD with suspected OSA/HS should always have polysomnography and, if necessary, prescribe appropriate treatment. In this regard, patients with COPD with suspected OSA/HS should always have polysomnography and, if necessary, prescribe appropriate treatment.

Polysomnography is a synchronous recording of electroencephalogram, electrooculogram (eyeball movement), submental electromyogram, airflow at the level of the mouth and nose, respiratory movements of the abdomen and chest, oxygen saturation of hemoglobin, electrocardiogram and leg activity [6]. This is the main method of investigating obstructive sleep apnea.

There is no effective drug treatment for OSA/HS. Patients hard tolerate surgical interventions (uvulo-palato-pharyngoplasty, septoplasty) and do not guarantee cure. Mechanical devices (intraoral applicators, devices for reposition of the lower jaw) are considered as a possible alternative to treatment using special breathing apparatus [6].

The method of choice in the treatment of this syndrome for more than 30 years has been the creation of continuous positive pressure in the upper respiratory tract, which prevents their obstruction and maintains sufficient permeability - CPAP-therapy (Continuous Positive Airway Pressure) [8]. It is prescribed if the severity of OSA/HS has reached moderate or severe levels. This method of treatment consists in the use of a special breathing apparatus, which creates a constant stream of air under pressure, which, acting through a mask, prevents the soft tissues of the upper respiratory tract from falling and prevents apnea and hypopnea.

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The purpose of this study was to analyze the frequency and severity of OSA/HS in patients with cerebral venous insufficiency on the background of chronic obstructive pulmonary disease and the level of hemoglobin saturation with blood oxygen at the time of an apnea.

II. Material and Methods

94 patients with COPD aged 40 to 75 years (68 men and 26 women) were examined. The average age of men was 56.5, women - 57.5 years. Criteria for inclusion in the study: age over 40 years, the presence of post-deduction parameters of respiratory function and clinical manifestations of breathing disorders during sleep (snoring, daytime sleepiness, respiratory arrest during sleep). According to the criteria of Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2010), middle stage COPD was diagnosed in 52, severe - in 42 cases. In accordance with the GOLD (2011) criteria, category B was determined in 18 patients (all cases of moderate degree of restriction of airflow), category C in 62 patients (34 - moderate, 28 - severe degree of restriction of airflow), category D - in 14 patients (all cases of severe airflow restrictions). Concomitant cardiovascular diseases (ischemic heart disease and arterial hypertension) were present in 69 patients (73.4%). Signs of cerebral venousdiscirculation (CVD) were in 61.4% of the subjects. The overwhelming majority of those examined had increased body weight: only 15 people (15.96%) had less than 25 kg/m^2 in body mass index (25 to 29 kg/m^2 in 21 people (22.34%)) (I the degree of obesity), in 29 people (30.85%) - from 30 to 40 kg/m^2 (II degree of obesity) and in 7 people (7.45%) - more than 40 kg/m^2 (III degree of obesity).

A polysomnographic survey was conducted at the MedcareEmbla S7000 Research Institute of Endocrinology, version 4.0 (copyright belong to MedcareFlaga, USA). CPAP - therapy was selected using the ResMed (Australia) S8 AutoSet Spirit II system. Statistical processing of the data obtained using nonparametric and parametric criteria.

III. Results

OSA/HS was confirmed in 21 patients (22.34%), in 31 cases only night snoring syndrome was recorded without stopping breathing and the oxygen saturation level of hemoglobin in the blood decreased. Among patients with only snoring without apnea, COPD of the middle stage was determined in 21, severe - in 10 cases; category B in 5, category C in 17, category D in 9 patients. The average indicator of forced expiratory volume in 1 second here was 51.3 ± 8.2% of the due, 6 people had concomitant cardiovascular diseases, the BMI was on average 26.1±2.9 kg / m2 (normal weight was registered in 15, I degree obesity - in 14, II degree obesity - in 2 people).

The mild OSA/HS was recorded in 3 people. The average number of respiratory disorders per night was 50.1±12.1, of which obstructive sleep apnea - 11.7 ± 2.4. The average duration of obstructive apnea was 26.4 ± 4.1 s, the average minimal oxygen saturation of hemoglobin with blood was 84.1 ± 10.3%, and the average saturation was 97.4±9.6%. COPD of the middle stage was determined in all patients of this group, category B - in one, category C - in two. The average indicator of the forced expiratory volume for the first was 42.4±7.1% of the due. Concomitant cardiovascular diseases were present in 2 people. 33.3% of the subjects had symptoms of venous dysgemia of the brain. The average BMI was 32.8±3.8 kg/m^2 (II degree obesity - in 2 patients) (Table 1).

Table 1: The degree of SOAGS depending on the presence in patients with IDC, obesity

OSA/HS n=21		Mild Degree		Moderate Degree		Severe Degree		Total		Surveyed without OSA/HS	
		n=3	%	n=11	%	n=7	%	n=21	%	73	%
COPD	Moderate Severity	3	14.3	4	19.0	0	0.0	7	33.3	67	91.8
	Severe Degree	0	0.0	7	33.3	7	100.0	16	76.2	6	8.2
CVD		1	33.3	8	72.7	7	100.0	16	76.2	26	35.6
Obesity	1st Degree	1	33.3	5	45.4	0	0.0	6	28.6	54	74.0
	2nd Degree	2	66.7	4	36.4	7	100.0	13	61.9	16	21.9
	3rd Degree	0	0.0	2	18.2	0	0.0	2	9.5	5	6.8

OSA/HS of moderate degree was recorded in 11 patients (including seven men): the average number of respiratory disorders per night was 140.4±25.1, of which obstructive apnea was 46.2±6.7, obstructive hypopnea was 91.4±9.8, and central apnea was 2.8±0.5. The average duration of obstructive apnea was 41.5±6.3 s, the average minimal oxygen saturation of hemoglobin with blood was 80.2±9.8%, and the

average saturation was 91.4±8.6%. COPD of the middle stage was determined in 4, severe - in 7 patients; category B - in 3, category C - in 5, category D - in 3 patients. The average indicator of forced expiratory volume with for the 1st second was 43.2±9.2% of the due. Concomitant cardiovascular diseases were present in 7 people. Symptoms of cerebral venous encephalopathy were observed in this group in 72.7% of cases. The average BMI was 33.4 ± 4.1 kg/m^2 (obesity grade I - 5, obesity grade II - 4, obesity grade III - 2 people).

OSA/HS severe was recorded in 7 people (including 5 men): the average number of respiratory disorders per night was 415.0±31.5, of which obstructive apnea was 270.6±24.5, obstructive hypopnea was 134.0±13.7, central apnea was 10.4±1.8. The average duration of obstructive apnea was 58.9±8.9 s, the average minimum saturation of blood hemoglobin with oxygen was 66.9±5.6%, the average saturation was 87.0±10.4% (the minimum level of saturation was 50%). Severe COPD was determined in all patients of this group; category B is not registered, category C was determined in 3, category D in 4 patients. The average indicator of forced expiratory volume for the 1st with was 39.2±6.9% of the due. Concomitant cardiovascular diseases were present in all patients. In this group, all patients had venous encephalopathy. The average BMI was 41.84±6.2 kg/m^2, and all patients were obese (II degree - in 7 people) (Table 1).

Taking into account the severity of OSA/HS and comorbid pathology, CPAP-therapy was recommended to 9 patients (42.85%), an ENT doctor's consultation - to 11 patients and a weight loss - to 15 patients. CPAP therapy was selected in 9 cases; 11 people refused it due to the high cost of treatment. During therapy, in 6 patients a decrease in the apnea/hypopnea index to 5 per hour was observed, which corresponded to the norm. In 1 patient, this index decreased to 9 per hour, which corresponded to the mild severity of OSA/HS (recommended selection of two-level PAP therapy).

It was found that the signs of cerebral venousdysgemia and obesity were significantly more common in the group of patients with OSA/HS of moderate severity and severe compared with the group of patients where SAIA was not detected.

No significant difference was found in the mean indices of the forced expiratory volume for the 1stwith a varying severity of OSA/HS and a reliable correlation connection of this indicator with the frequency of apnea. However, with similar comparisons with BMI values, there was a significant direct correlation with the severity of OSA/HS, as well as a significant correlation between BMI and the amount of apnea (r=0.7) and the oxygen saturation level of hemoglobin (r = –0.6). Apparently, in the occurrence of OSA/HS, the degree of obesity is more important pathogenetically than the degree of obstruction of the lower respiratory tract. The high incidence of OSA/HS in patients with increased body weight in COPD is probably a feature of the so-called obesity COPD phenotype.

IV. Conclusion

Based on the foregoing, it can be concluded that OSA/HS is one of the important mechanisms that make heavier the course of COPD, especially in individuals with increased body mass, and requires mandatory correction of the upper airway patency using CPAP-therapy. For persons with OSA/HS, the formation of cerebral venousdysgemia is also characteristic, which significantly aggravates the course of the underlying disease and increases hypoxemia. For the non-removal of neurological symptoms in patients with COPD, in particular in patients with OSA/HS, course of venotonic drugs should be prescribed.

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Global Journal of Medical Research: F
Diseases
Volume 19 Issue 1 Version 1.0 Year 2019
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Tuberculosis Detection among Children with Human Immunodeficiency Virus Infection using Osborne's Criteria

By Subhashchandra Daga, Vikram Kumar, Sandeep B Patil & Madhuri P. Agrawal

Abstract- The mortality due to tuberculosis is high among the human immunodeficiency virus (HIV)-infected children. A confirmative diagnosis of tuberculosis is difficult to obtain, especially in a resource-limited setting. A clinician might, therefore, go for the diagnostic criteria with higher sensitivity to avoid under-diagnosis and delayed treatment. The diagnosis of probable tuberculosis by Osborne's method is a good option in such a situation. The present study includes 42 HIV-infected subjects diagnosed with probable tuberculosis using Osborne's method. During a treatment period of 6-9 months; 39(91%) "felt better", 28(67%) gained weight and 2 (4.7%) died.

GJMR-F Classification: NLMC Code: WF 200

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Tuberculosis Detection among Children with Human Immunodeficiency Virus Infection using Osborne's Criteria

Subhashchandra Daga [α], Vikram Kumar [σ], Sandeep B Patil [ρ] & Madhuri P. Agrawal [ω]

Abstract- **The mortality due to tuberculosis is high among the human immunodeficiency virus (HIV)-infected children. A confirmative diagnosis of tuberculosis is difficult to obtain, especially in a resource-limited setting. A clinician might, therefore, go for the diagnostic criteria with higher sensitivity to avoid under-diagnosis and delayed treatment. The diagnosis of probable tuberculosis by Osborne's method is a good option in such a situation. The present study includes 42 HIV-infected subjects diagnosed with probable tuberculosis using Osborne's method. During a treatment period of 6-9 months; 39(91%) "felt better", 28(67%) gained weight and 2 (4.7%) died.**

I. Text

Of the estimated 7.5 million cases of tuberculosis; 650,000 (9%) have occurred in children1. The estimates have limitations since there are difficulties in establishing a definitive diagnosis of tuberculosis more so when associated with HIV infection. The symptoms of childhood tuberculosis are non-specific, the radiographs are difficult to interpret, and a bacteriological confirmation is rarely achieved. In view of this, we have studied the effect of treatment on the probable cases of tuberculosis as categorized by Osborne's method 2.

The present study was conducted at the pediatric outpatient department of Sassoon General Hospital, Pune. The hospital, a tertiary care center, is also a regional center for antiretroviral therapy (ART). One hundred and eighty eight patients with tuberculosis, registered at the outpatient department, were studied. The demographic data and clinical details were collected in a pre-determined format. A diagnosis of probable tuberculosis was made when a child with suspected tuberculosis had any of the following: a positive Mantoux test, suggestive radiological findings, suggestive histological appearance in biopsy and a favorable response to the anti-tuberculosis treatment 2. The subjects of this study were the cases of probable tuberculosis with age above 18 months and a positive ELISA test for HIV infection. The presenting complaints, clinical features, chest radiograph findings and Mantoux test results were recorded. The nutritional status was graded as per Indian Academy of pediatrics guidelines 3. The parameters of subjective and objective improvement were identified. The subjective improvement meant better activity, better appetite and feeling of wellness and the objective improvement was indicated by a weight gain and a change in nutrition grade, if any, during monthly visits.

As shown in the table, of the 188 subjects, 42 (25%) had a positive ELISA test for HIV infection. The cases of probable tuberculosis were more common among the boys and in the age group 6-10 years. Severe malnutrition was observed in 40.5%. After the treatment, 39 (91%) demonstrated a subjective improvement, substantial weight gain was observed in 47.5%. Nutrition grade changed from IV to III in 8 (19%), III to II in 7(16.6%), II to I in 4 (9.5%), I to normal in 4 (9.5%), and it remained unchanged in 16 (38%). The Mantoux test was positive, more than 5 mm, in 13 (30.9%) cases. An intrafamilial contact with an adult case of pulmonary tuberculosis was observed in 19 (45.5%). The chest radiograph findings were as follows: normal-5 (11.9%), mediastinal adenopathy- 20 (47.6%), parenchymal lesions- 11 (26.1%) and a miliary disease- 6 (14.2%).

The mortality has been reported to be six times higher among HIV infected- children with tuberculosis4. The conventional criteria result in under-diagnosis and under-treatment of tuberculosis in children, more so in presence of HIV infection. In view of a high mortality among untreated children, the treatment needs to be offered not only to bacteriologically confirmed cases, but to also to most likely cases, even at the risk of some over-treatment.

The published studies of children with tuberculosis in sub-Saharan Africa and elsewhere have shown a co-infection rate (with HIV) of 11-64%5. A high proportion of HIV infection among our subjects is largely because ours is a tertiary care center and also a regional center for ART. A smaller proportion of under-fives may be a reflection of initiative against mother-to-child-transmission (MTCT) taken up on a large scale. Secondly, deaths due to unrecognized and untreated Pneumocystis pneumonia among younger children may also be responsible for this finding6. A co-existence of

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PEM and the response to treatment in terms of a weight gain and a change in nutrition grade has been on expected trails. The presence of intra familial contact in 45% cases may, in fact, be included among the diagnostic criteria. The studies have found that the mothers with tuberculosis are important source of tuberculosis transmission to children7.

Points to remember

1. Definitive diagnosis of childhood tuberculosis is difficult especially in children with human immunodeficiency virus infection.
2. Osborne's classification of childhood tuberculosis is useful in detecting probable cases.
3. This avoids under diagnosis and delayed treatment.

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Table 1: Distribution of parameters

1. Age		
Up to 5 years	2	4.7
6-10 years	26	61.9
11-15 years	14	33.3
2. Gender		
Male	25	59.5
Female	17	40.5
3. Nutritional Status		
Normal	4	9.5
Grade I PEM	5	11.9
Grade II PEM	16	38
Grade III PEM	14	33.3
Grade IV PEM	3	7.2
4. Mantoux Test		
Positive	13	45.5
Negative	29	54.5
5. Intrafamilial Contact		
Present	19	45.5
Absent	23	54.5
6. Chest X ray Findings		
Normal	5	11.9
Mediastinal adenopathy	20	47.6
Parenchymal disease	11	26.1
Miliary lesions	6	14.2

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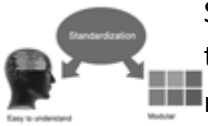

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Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.

Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

The Administration Rules

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

Please read the following rules and regulations carefully before submitting your research paper to Global Journals Inc. to avoid rejection.

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Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

Criterion for Grading a Research Paper (Compilation) by Global Journals

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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ISSN 9755896