

Palestine Health Research Results

Hematology & oncology



المقدمة:

يعتبر البحث العلمي من أهم الأنشطة الإنسانية التي يمارسها الإنسان فوق سطح كوكب الأرض في هذا العصر وفي العصور السابقة، وقد كان البحث العلمي على مر الأزمنة أساس النهضات والتقدم والتطور، وما ننع به اليوم من رقي وحضارة هو نتاج البحث العلمي المستمر بمختلف مجالاته.

ويعرف البحث الصحي بأنه كل جهد علمي منظم يهدف إلى تنمية المعرفة و المهارات في المجالات الصحية المختلفة و إيجاد الطرق الأفضل للوقاية والعلاج من الأمراض وكذلك تطوير نظام صحي قادر على الاستجابة بفعالية ونجاعة لاحتياجات السكان في ظل بيئة صحية ديناميكية.

وأيضاً فإن البحوث الصحية يمكن أن توفر معلومات هامة حول اتجاهات الأمراض وعوامل الخطر، ونتائج البرامج أو التدخلات الصحية العامة، وأنماط الرعاية المختلفة وتكاليف الرعاية الصحية واستخدامها، وكذلك يمكن أن توفر معلومات هامة حول فعالية التدخلات الطبية والجراحية، وتحسين استخدام الأدوية واللقاحات، أو تطوير الأجهزة الطبية، وطرق التشخيص.

كما أنها حيوية لتسجيل وتقييم الخبرة في الممارسة السريرية من أجل وضع مبادئ توجيهية لأفضل الممارسات وضمان الرعاية العالية الجودة للمرضى.

ونحن في وزارة الصحة وإدراكاً منا للدور الهام للبحث العلمي وكذلك للمسؤولية والدور المناط بنا في قيادة مسار التطوير والتدريب أتحنا الفرصة للباحثين وطلبة كليات الطب والصيدلة والعلوم الطبية الأخرى لعمل الأبحاث والتدريب في مرافق وزارة الصحة المختلفة ضمن الضوابط والقوانين المنظمة والمعمول بها من أجل تحقيق الهدف والنهوض بالقطاع الصحي من خلال دعم التعليم الطبي والبحث الصحي. ونحن في الإدارة العامة لتنمية القوى البشرية نقوم بتنظيم ومتابعة هذا النشاط البحثي من خلال دائرة البحث الصحي التي تقوم في هذا المجال بـ:

- الإشراف علي هذا النشاط البحثي داخل مرافق الوزارة
 - توجيه الباحثين للأماكن التي سيقومون بتنفيذ الأبحاث بها
 - التأكد من الإجراءات التي تحفظ حقوق المبحوثين
 - تدقيق الجانب الأخلاقي من الأبحاث
 - الحفاظ على ممتلكات الوزارة.
 - توثيق الأبحاث التي يتم انجازها
 - توصيل نتائج البحوث لذوي العلاقة والمهتمين وصناع القرار في الوزارة.
 - عمل الإحصائيات والتقارير المتعلقة بالأبحاث
- لكن يبقى السؤال الملح وهو كيف يمكن الاستفادة من هذه الأبحاث ونتائجها في تطوير وتحسين الخدمات الصحية؟

لذلك قمنا بإنشاء صفحة على شبكة الانترنت (ضمن موقع الوزارة) خاصة بعرض ملخصات البحوث التي تجرى في الوزارة، كما قمنا بتصنيف رسائل الماجستير (التي حصلنا عليها من الجامعات و الباحثين) إلى عدة موضوعات وقد بدأنا بإعداد مجلة تشمل ملخصات الرسائل العلمية ونتائجها وتوصياتها من أجل توصيلها لذوي العلاقة والمهتمين وصناع القرار في المستويين الطبي والإداري.

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Thiopurine Methyltransferase Genotyping in Childhood Acute Lymphoblastic Leukemia Patients in Gaza Strip

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Abstract

Background

The genetic polymorphism of thiopurine methyltransferase (TPMT) is well characterized in most populations. Three common polymorphic alleles are associated with impaired activity of the enzyme. These are TPMT*2 (238G>C), TPMT*3A (460G>A, 719A>G) and TPMT*3C (719A>G).

Objective

The aim of the present study was to determine the frequency of the functional TPMT polymorphisms and their association with the occurrence of adverse events, during 6-mercaptopurine therapy in pediatric acute lymphoblastic leukemic (ALL) patients in Gaza Strip.

Methods

A total of 56 DNA samples from all pediatric ALL patients admitted to the pediatric hematology departments of Gaza strip hospitals were analyzed.

Genomic DNA from peripheral blood leukocytes was isolated and the TPMT*2, TPMT*3A and TPMT*3C allelic polymorphism was determined by PCR- RFLP and allele specific PCR technique.

Results

No TPMT*2, *3C mutant alleles were detected. Only the TPMT*3A allele was detected in one patient out of 56 DNA samples of pediatric ALL patients in Gaza strip. Thus, frequency of TPMT*3A allele was 0.89%. Fourteen patients of ALL were suffering from mylototoxicity during 6MP therapy. From our results, no significant association could be established between clinical and laboratory data and/or the presence of the mutation in TPMT gene. The calculated incidence of ALL in children in Gaza Strip is 2 cases per 100000 children.

The incidence of ALL is higher in males than in females. The mean age of ALL incidences in Gaza Strip is 4.4 ± 2.6 years.

Conclusion

This is the first analysis of the polymorphisms of the TPMT gene in childhood ALL patients in Gaza Strip. Other types of mutation in TPMT gene may be responsible for the observed myelotoxicity among the investigated patients.

Factors other than TPMT polymorphisms may also be responsible for the development of toxicity. Therefore, more studies are recommended to be performed in order to investigate such factors.

Keywords: Polymorphisms, Thiopurine *S*-methyltransferase, Gaza Strip, Acute lymphoblastic leukemia

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

The present study is the first analysis of the polymorphisms of the TPMT gene in acute lymphoblastic leukemic childhood patients in Gaza strip.

TPMT*3A was the only deficiency alleles detected in the pediatric ALL patients in Gaza strip with an allelic frequency of 0.89%.

TPMT mutations are not associated with myelosuppression in ALL pediatric patients in Gaza strip.

Other types of mutation in TPMT gene may be responsible for myelotoxicity or factors other than TPMT polymorphisms may be responsible for the development of toxicity.

On light of our study and others, myelosuppression due to 6 mercaptopurine treatment is not always associated with TPMT gene mutations while the determination of the TPMT genotype may be useful for predicting myelosuppression in patients with TPMT homozygotes and heterozygotes.

6.2. Recommendations

Even in ALL patients with a wild TPMT genotype, clinicians should pay attention for the possible development of myelosuppression.

Further studies with more participants and analyzing more TPMT and/or other metabolizing enzymes alleles, will be needed to establish a nation wide pretreatment strategies among patients in Gaza Strip.

Molecular, biochemical and hematological investigations of β -thalassemic children in Gaza governorate

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Abstract

Background: Thalassemias are hereditary anemias mostly common in the Mediterranean, the equatorial, or near equatorial regions of Africa and Asia.

They are classified according to which particular globin chain(s) is/are produced in a reduced amount: α , β , $\delta\beta$, δ , and $\gamma\delta$ thalassemias. In the Gaza Strip, more than 300 patients have been diagnosed with β -thalassemia major, they are currently being transfused and managed in local hospitals.

Aims: To investigate molecular, biochemical and hematological aspects of β -thalassemic children aged 5-12 years in Gaza City.

Methodology: Blood samples were collected from 53 β -thalassemic children who are transfused and managed at the pediatric hospitals at Gaza City. Blood withdrawals were performed just before the scheduled blood transfusion. In addition blood samples were also collected from 53 apparently healthy children. Cases and controls were age and sex matched. Part of data was collected by using close-ended questionnaire. Complete blood count and biochemical tests were performed. Screening for possible mutations in HBB gene was performed at the molecular medicine laboratories of the Bernhard Nocht Institute (BNI), Germany, according to Dynamic Allele-Specific Hybridization (DASH) method. This work was performed according to the cross-sectional descriptive study design. An official approvals letters were obtained from Helsinki committee at the Palestinian ministry of health and from the Palestinian Thalassemia Center who approved performing the study on the thalassemic children. The data were tabulated, encoded and statistically analyzed using the IBM SPSS Statistics (version 17, IBM Corporation, Somers, NY). The Chi square test, the independent-samples ttest, and One-Way analysis of variance (ANOVA) were performed aiming at the description, identification of significant relationship, correlations and differences between the study items, variables and parameters. A p -value < 0.05 was considered statistically significant.

Results: A significant difference was reported in the parents' consanguinity of the two groups ($P=0.001$). About 71% of the β -thalassemia major children parents are 1st degree cousins compared to the control group where the percentage is $<2\%$. Severe anemic presentations were seen in the patients where hemoglobin is dropped to about 30% of the level reported in controls, 8.0 ± 1.0 vs 11.4 ± 0.8 g/dL, respectively. Microcytosis without hypochromia is significantly noticeable in patients than controls with MCV and MCH values of 75.9 ± 7.3 fl and 24.1 ± 2.3 pg in patients compared to 79.5 ± 4.4 fl and 24.7 ± 2.2 pg in controls. In addition, a significantly secondary thrombocytosis and leukocytosis were reported in patients. The biochemical characteristics showed significantly deteriorated liver and kidney function tests except for urea in patients as compared to controls. The protein contents: total protein, albumins, globulins are significantly reduced in patients. Moreover, there is iron overload in patients as compared to controls with serum ferritin reached 3231.0 ± 1560.5 ng/l vs 46.8 ± 23.1 ng/l ($P < 0.0001$). The molecular characterization revealed that IVS-I-110 was found nearly in quarter (24/106, relative allele frequency of 0.23) of the patients' chromosomes, followed by IVS-I-1, and CD39 which found in 18 and 17 patients' chromosomes, with relative allele frequency 0.17 and 0.16 respectively. Less frequent mutations IVS-I-6 and CD37 were found with relative allele frequency of 0.08 and 0.06, respectively.

Conclusions: There is a molecular heterogeneity of the HBB mutation among thalassemic patients of the Gaza Strip. A deteriorated hematological and biochemical pictures were seen in the patients which requires more appropriate management protocol for those patients specially with the severe mutation.

Keywords: β -thalassemia, Children, Molecular, Biochemical and Hematological Parameters, Gaza governorate.

Conclusions and Recommendations

Conclusions

- 1- About 71 % of the β -thalassemia major children parents are 1st degree cousins compared to the control group where the percentage is less than 2.0 %.
- 2- All hematological characteristics, except for MCH, measured in the present work revealed significant differences between patients and controls.
- 3- A severe anemic presentations were seen in the patients as compared to the controls. The hemoglobin level in patients is dropped to about 30 % of the level reported in controls.
- 4- A significantly remarkable secondary thrombocytosis (thrombocythemia) and leukocytosis were reported in patients compared to controls.
- 5- A significantly deteriorated liver and kidney function tests, except for urea, were reported in patients as compared to controls.
- 6- The protein contents: total protein, albumins, globulins are significantly reduced in patients as compared to control group.

- 7- There is iron overload in patients as compared to controls with serum ferritin reached 3231.0 ± 1560.5 ng/l vs 46.8 ± 23.1 ng/l ($P < 0.0001$).
- 8- Serum calcium level was significantly reduced where as serum phosphorus showed no significant difference in patients compared to controls.
- 9- More than 58 % of the patients showed a poikilocytosis score of 4-5.
- 10- The β^+ mutation IVS-I-110 was found nearly in quarter of the patients' chromosomes, followed by β^0 mutation IVS-I-1, and β^0 CD39.
- 11- Less frequent mutations IVS-I-6 and CD37 were found but at low relative allele frequency.
- 12- Patients homozygous for the IVS-I-6 variant exhibited a significantly different hematological characteristics compared to other genotypes.
- 13- The homozygous for IVS-I-110 showed a very deteriorated liver function tests in terms of ALT and AST, while homozygous for IVS-I-6 showed a high serum urea concentration as compared to other genotypes.

Recommendations

- 1- Molecular screening for all thalassemic patients is recommended which may result in modification to a more appropriate management protocol for those patients specially with the severe mutation.
- 2- Educational and awareness programs aiming to provide the population with the risks for consanguineous marriages on the kids and the generations are highly needed.

**Immunological assessment of α -thalassemic major children
aged 5-12 years old attending Abd El-Aziz El-Rantisy Hospital in
Gaza strip**

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Abstract

Background: Beta-thalassemia major patients suffer from many problems rather than severe anemia. Immune abnormalities have been suggested as a precipitating factor for the fourth most common cause of death in α -thalassemia.

These abnormalities have been attributed both to the disease itself and to the applied therapeutic intervention.

Objective: to assess some immunological parameters in children aged 5-12 years old with α -Thalassemia major in Gaza Strip.

Materials and methods: this case-control study comprised 43 β -thalassemic major children aged 5-12 years old attending Abd El-Aziz El-Rantisy hospital and 43 healthy children served as controls. Cases and controls were matched for age and sex. Blood samples were collected by a well-trained nurse from thalassemic children just before a scheduled transfusion of packed red blood cells and also from controls.

Complete blood count (CBC) was done in the same day of collection. Serum levels of interleukin-1- β (IL-1- β), interleukin-6 (IL-6) and tumor necrosis factor- β (TNF- β) cytokines, immunoglobulins IgG, IgA and IgM, complements C3,C4, ferritin and reactive protein(CRP) were determined.

Results: the average age of the study population was 7.9 ± 2.2 years. Most patients 29 (67.4%) had allergic reactions. Discharge of desferrioxamine was intramuscular in 25 (58.1%) patients and subcutaneous in 17 (39.5%) patients, one patient (2.3%) refused iron chelation therapy. In general primary and secondary blood indices were significantly decreased in thalassemic children compared to controls. The total white blood cell (WBCs) and lymphocytes (LYMP) were significantly increased in patients compared to controls (8.9 ± 2.1 V.s 7.9 ± 2.0 $\times 10^3$ cell/ μ l, $p=0.025$ and 3.6 ± 0.9 V.s 3.1 ± 0.79 $\times 10^3$ cell/ μ l, $p=0.003$, respectively). WBCs and LYMP significantly decreased with allergic reactions (8.5 ± 2.2 V.s 9.9 ± 1.6 $\times 10^3$ cell/ μ l, $p=0.042$ and

3.4±0.9 V.s 4.0±0.9 X10³cell/il, p=0.050, respectively). Ferritin level in patients was markedly higher than in controls (3138.0±1041.5 V.s 17.3±2.5 ng/ml, p=0.000). Ferritin level showed positive association with age and allergic reaction. Complements 3 and 4 reduced significantly in thalassemic children (118.7±12.4 V.s 136.6 ±23.3 mg/dL, p=0.000 and 49.3±13.4 V.s 62.3±21.6 mg/dL, p=0.001, respectively), regardless of allergic reaction, age, ferritin level and CRP. IgM and IgA were within the normal levels compared to control. However lower level of IgG was found in patients. Higher levels of IgG, IgM and IgA were found with increasing age and in positive CRP patients (p<0.05). On the other hand, immunoglobulins neither had a relation with ferritin nor with allergic reactions. Cytokines were normal that they almost showed undetected levels in controls and patients (TNF-β: 56.1 and 97.7%, IL-6: 95% and 88.4%, and IL-I-β: 100% for both controls and patients). C-reactive protein status didn't differ significantly between controls and cases.

Keywords: β-thalassemia, Children, Gaza strip, Immunological assessment.

Conclusions and Recommendations

Conclusions

1. The Study population comprised 24 (55.8%) males and 19 (44.2%) females with average age of 7.9±2.2 years.
2. Most of patients 29 (67.4%) had allergic reactions.
3. Desferrioxamine is the standard iron chelator used in Gaza Strip. Discharge of this chelator was intramuscular in 25 (58.1%) patients and subcutaneous in 17 (39.5%) patients.
4. In general primary and secondary blood indices were significantly decreased in thalassemic children compared to controls.
5. The total white blood cell and lymphocytes were significantly increased in patients compared to controls (8.9±2.1 V.s 7.9±2.0, p=0.025 and 3.6±0.9 V.s 3.1±0.79, p=0.003, respectively). When related to age, total white blood cell and lymphocytes showed no significant difference. However, they significantly decrease with allergic reactions (8.5±2.2 V.s 9.9±1.6, p=0.042 and 3.4±0.9 V.s 4.0±0.9, p=0.050, respectively).
6. Ferritin levels in patients were markedly higher than in controls (3138.0±1041.5 V.s 17.3±2.5 ng/ml, p=0.000), reflecting iron overload despite of desferrioxamine treatment. Ferritin levels showed positive relations with age and allergic reaction.
7. Complements 3 and 4 reduced significantly in thalassemic children (118.7±12.4 V.s 136.6 ±23.3 mg/dL, p=0.000 and 49.3±13.4 V.s 62.3±21.6 mg/dL, p=0.001, respectively), regardless of allergic reaction, age, ferritin level and CRP.
8. IgM and IgA of patients were in normal levels compared to controls. However, lower level of IgG was found in patients. Higher levels of IgG, IgM and IgA were found with increasing age and in positive CRP patients (p<0.05). On the other hand, immunoglobulins neither had a relation with ferritin nor with allergic reactions

9. Cytokines were normal that they almost showed undetected levels in controls and patients (TNF- β : 56.1 and 97.7%, IL-6: 95% and 88.4%, and IL-I- β : 100% for both controls and patients), reflecting the absence of acute immune abnormalities.
10. C-reactive protien status didn.t differ significantly between controls and cases.

Recommendations

1. The patients should be regularly tested for antibodies screening.
2. Transfusion transmissible infections (TTI) test should be carried out.
3. Some testes must be activated in blood transfusion centers as antibody screening for blood donors.
4. Washed red cells is highly recommended to be transfused to the blood transfusion dependent patients especially thalassemic patients.
5. New stratigies of chelation using other iron chelator drugs such as deferasirox (ICL670, Exjade) and deferiprone are recommended.
6. Providing easy access to the drug discharge pump for all patients and its instant repair when broken.
7. Improvement of blood transfusion program in terms of increase frequency and units of transfused blood to improve hemoglobin level in thalassemic patients.
8. Further studies are recommended on:
 - a) Cellular immunity including response of memory T cells and specific antigenic stimuli responsible for infections in thalassemic patients.
 - b) Immunological abnormalities in older thalassemic patients.
 - c) Assessment of IgE which could be useful in case of allergy.
 - d) Evaluation of other cytokine in thalassemic patients.

Blood Levels of Protein C among Intensive Care Unit Patients in Gaza, Palestine

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Abstract

Background: Intensive care unit (ICU) is one of the largest, most expensive, and complex components of health care. However, assessment of protein C (PC) and C-reactive protein (CRP) concentrations in ICU patients may help in identifying high risk groups and potential therapeutic targets.

Objective: To estimate the PC levels and CRP among ICU patients and their relations to ICU outcome.

Methods: This observational cross sectional study, in Al-Shifa hospital ICU, included 85 patients, and 85 healthy controls. Plasma PC concentrations, and CRP levels were measured. Kidney and liver dysfunctions were assessed biochemically, in addition, coagulation tests were performed.

Results: PC levels were below the lower limit of normal in 65.9% of patients (n=56) at admission, irrespective of the presence primary diagnosis and sex.

PC levels were lower in non survivors (n=17 ; 20%) than in survivors. There was significant correlation between PC levels and ICU outcome (P=0.001).

Patients with high CRP levels upon ICU admission had higher mortality rates than patients with normal levels. There was no significant correlation between CRP levels and ICU outcome (P=0.856).

Conclusion:

PC concentrations are generally low in ICU patients. PC levels were also associated with organ dysfunction/failure and were independently associated with a higher risk of ICU mortality. CRP levels are considered as a good early marker of morbidity and mortality in these patients. In addition, CRP concentrations may be a valuable addition to predict the risk of death.

Keywords: C-Reactive Protein, Gaza Strip, Intensive care unit, Protein C.

Conclusions

Our study demonstrates that PC concentrations are generally low in ICU patients. PC levels were associated with organ dysfunction/failure and were independently associated with a higher risk of ICU mortality. These findings suggest that targeting the PC pathway may improve outcomes in patients with multi-organ failure of non septic origin.

The study demonstrated an important link between low PC levels and patients with failing organs and those at risk of dying.

The study confirmed that baseline PC levels are dependent predictor of outcome in ICU patients.

Lower PC levels were common in ICU patients and were associated with several severely negative clinical outcomes, including increased mortality.

These findings suggest that PC levels can be used prognostically and that such agents as PC, or preferably, activated PC, may reverse the acquired PC deficiency and improve outcome.

Recombinant PC may be a new target for therapy for patients with non –infectious-induced organ failure/dysfunction in the ICU.

Abnormal three coagulation markers together (PT, PTT, PLT) coincide with low levels of PC.

This is to the best of our knowledge the first study that evaluates risk factors for the development of ARF in a subgroup of ICU patients; additionally, the incidence of ARF in this patient population are described.

C-reactive protein levels were good early marker of morbidity and mortality in our patients. In addition, CRP concentrations may be a valuable addition to predict the risk of death. Yet there were more deaths in the group with higher CRP levels than in the other two groups who had CRP levels <40 mg/dL.

Recommendations

Introduction of PC testing as a routine in ICU at admission and consequently. Treatment with recombinant PC could offer a new way of interrupting the progression to sepsis and organ failure in high risk patients.

Serial measurements of CRP concentrations in critically ill patients may help to identify patients who may require more aggressive diagnostic and therapeutic interventions to avoid complications. CRP concentrations may also be helpful in clinical trials, to identify high-risk patients who would benefit from new therapeutic interventions.

Further research is needed dealing with large number of cases with emphasis on PC levels, CRP and coagulation markers.

Clinical trials are proposed to evaluate the role of recombinant PC in treatment of critically ill patients in our area.

Allele and Genotype Frequencies of the ABO Blood Group System in a Palestinian Population

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Abstract

The ABO blood group antigens are of clinical importance in blood transfusion, organ transplantation, autoimmune hemolytic anemia and fetomaternal blood group incompatibility. The *ABO* locus are located on chromosome 9. Till now, more than 200 *ABO* alleles have been identified by molecular investigations. The objective of this study was to determine the major *ABO* alleles' and genotypes' frequencies in a Palestinian population residing in Gaza Strip. A four separate-reaction multiplex allele specific polymerase chain reaction (AS-PCR) was used to determine the ABO genotypes. Our study population consisted of 201 unrelated subjects (50 males and 151 females) whose DNA extracted from peripheral blood was subjected to genotyping.

The genotypes of 201 samples were found to be A_1A_1 (n=3), A_1O_1 (n=24), A_1O_2 (n=25), A_1A_2 (n=4), A_2A_2 (n=2), A_2O_1 (n=13), A_2O_2 (n=2), B_1B_1 (n=5), B_1O_1 (n=26), B_1O_2 (n=14), A_1B (n=11), A_2B (n=4), O_1O_1 (n=31), O_1O_2 (n=26) and O_2O_2 (n=11), from which the deduced phenotypes were A (n=73), B (n=45), AB (n=15) and O (n=68). Moreover, there was no significant difference between observed and expected genotypes and the genotyping results were consistent with Hardy-Weinberg law. The frequencies of A_1 , A_2 , B_1 , O_1 and O_2 alleles were: 0.174, 0.067, 0.162, 0.376 and 0.221 respectively. The rare *cis-ABO₁* allele was not encountered in the study population. The genotype results were compared with serologically determined phenotypes and there were no deviation. To our knowledge, this is the first study in Gaza strip investigating the ABO genotypes. ABO genotyping has practical applications in blood transfusion, tissue/organ transplantation, blood typing discrepancies and forensic/paternity testing investigations.

Key words: *ABO alleles ; ABO genotypes ; AS-PCR; allele frequencies ; ABO phenotype .*

Conclusion and Recommendations

The present study focused on detection of the major ABO genotypes in a Palestinian population residing in Gaza Strip. The results of this study can be summarized as follows:

1. In Gaza Strip , the A phenotype was the most common blood group followed by O,AB and B.
2. The frequencies of *ABO* alleles in the investigated subjects were 0.25 for *IA*, 0.17 for *IB* and 0.58 for *IO*. These frequencies are comparable to those obtained from ABO genotyping.
3. No statistically significant differences were found between the frequency of observed and expected genotypes .This proved that the ABO genotypes of the randomly collected samples were in Hardy- Weinberg equilibrium data.
4. Molecular data indicated that Hardy-Weinberg equation can be used to detect the percentage of the major blood group in our population .
5. The distribution of the ABO genotypes in Gaza Strip population is similar to that of many Asian populations.
6. There is no significant difference between male and female in terms of ABO phenotypes .
7. Our study indicated that the most common genotype is *OIOI* and the lowest are *A2A2* and *A2O2*. The *cis ABOI* was not encountered.
8. The homozygous genotype of *A* and *B* alleles (*AA* , *BB*) were less than the heterozygous(*AO*, *BO*) genotype.
9. The frequency of *O2* allele in Gaza strip seems to be higher than that reported in many neighboring countries .

This study determined the exact phenotypic frequency of ABO blood groups in Gaza Strip and the frequencies of the prevalent *ABO* alleles namely, *A1*, *A2*, *B1*, *O1* and *O2*. When both serological typing and ABO genotyping are performed and full compatibility between a phenotype and a genotype is observed, examiners can determine the ABO phenotype with an even higher level of confidence. Therefore, we recommend that the health care system in Palestine adopt ABO genotyping particularly for cases of discrepant blood phenotypes.

Hepcidin Status Correlated with Biochemical Parameters among Iron Deficient Anemic Children aged (6 – 12) Years in Gaza City

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Abstract (English)

Background: Hepcidin is a small cysteine-rich peptide hormone produced in the liver.

Hepcidin is also a tightly folded polypeptide containing 25 residues in length and is 32% beta sheets. This molecule regulates the absorption of iron in the body. It was discovered in 2000. Recent studies demonstrated that hepcidin is a master iron regulator. Therefore, assessment of hepcidin status and clarifying its association in iron deficiency anemia (IDA) could constitute a promising therapy of the disease.

Objective: To correlate hepcidin status with some biochemical parameters among IDA children aged 6 – 12 years in Gaza City.

Materials and Methods: This case-control study comprised 80 IDA children and 80 apparently healthy non IDA children controls. Questionnaire interviews were applied. Serum hepcidin and serum ferritin were measured by ELISA. Serum iron, and TIBC were determined photometrically. Complete blood count (CBC) was also performed by [Cell-Dyn-1800] autoanalyser. Transferrin and transferrin saturation were calculated.

We obtained a permission from local ethical committee to conduct this study. Overall data were computer analyzed using SPSS package version 20.0. .

Results: The mean serum iron, transferrin saturation and serum ferritin in cases were significantly lower than that in controls (48.4 ± 16.3 $\mu\text{g/dL}$, 13.8 ± 6.3 % and 13.4 ± 7.2 ng/ml vs. 80.7 ± 21.3 $\mu\text{g/dL}$, 25.9 ± 7.4 % and 20.6 ± 12.7 ng/ml) with $P=0.000$. Hepcidin was found to be significantly associated with family income and children physical activity. The mean level of serum hepcidin was significantly lower in IDA children compared to healthy non IDA children controls (4.8 ± 5.7 and 8.0 ± 6.7 ng/ml, $P=0.001$). The Pearson correlation test showed negative significant correlations between hepcidin levels and serum iron ($r=-0.232$, $P= 0.003$), and positive significant

correlations with serum ferritin ($r=0.320$ $P=0.000$). The mean TIBC and transferrin in cases were significantly higher than that in controls (367.9 ± 41.4 $\mu\text{g/dL}$ and 262.1 ± 29.5 mg/dL vs 315.6 ± 38.9 $\mu\text{g/dL}$ and 224.9 ± 27.7 mg/dL) with $P=0.000$. The Pearson correlation test showed negative significant correlations between hepcidin levels and TIBC and transferrin ($r=-0.172$, $P=0.030$, $r=-0.168$, $P=0.033$, respectively). The average values of RBC, Hb, HCT, MCV, MCH and MCHC were significantly lower in IDA children (4.6 ± 0.7 , 10.3 ± 0.5 g/dl , 32.2 ± 2.5 , 71.1 ± 8.8 , 22.9 ± 3.4 and 32.0 ± 1.7 , respectively).

Compared to controls (4.8 ± 0.4 , 12.0 ± 0.7 g/dl , 35.8 ± 2.1 , 75.6 ± 4.7 , 25.7 ± 2.0 and 33.4 ± 1.6 , respectively with $P=0.000$). On the other hand, RDW was significantly higher in cases vs controls (14.8 ± 2.6 vs 13.7 ± 0.8 , with $P=0.000$). Pearson correlation test also showed positive significant correlations between hepcidin levels and RBC and Hb.

Conclusions: The mean level of hepcidin was significantly lower in cases compared to controls. Hepcidin levels were significantly higher among children whose parents were more educated and employed, as well as high income families. IDA was more prevalent among children whose parents have a lower education level and unemployed, as well as in families with less income and individuals with family history of IDA. Hepcidin is strongly correlated with serum iron, transferrin saturation and serum ferritin. Thus it is considered as a good marker and promising therapeutic agent of IDA. Thus; It is recommended to introduce hepcidin hormone assay for IDA in our area, and conduct further research related to the relationship of hepcidin hormone with IDA.

Keywords: *Hepcidin, Serum Iron, Ferritin, Iron deficiency Anemia, Gaza.*

Conclusions and Recommendations

Conclusions

1. The mean ages of cases and controls were 6.8 ± 0.81 , 9.5 ± 0.51 , 11.5 ± 0.58 years old.
2. IDA was more prevalent among children whose their parents have a lower education level and unemployed, as well as in families with less income and individuals with family history of IDA.
3. The average levels of serum iron, transferrin saturation and serum ferritin were significantly lower in cases compared to controls. In contrast, TIBC and transferrin was higher in cases compared to controls.
4. The mean level of hepcidin was significantly lower in cases compared to controls.
5. Hepcidin levels were significantly higher among children whose their parents were more educated and employed, as well as high income families.
6. There were negative significant associations between hepcidin levels with TIBC, serum iron, transferrin and transferrin saturation, and positive significant association between hepcidin and serum ferritin.

Recommendations

1. Introducing hepcidin hormone test for IDA and anemic patients in Gaza hospitals as a diagnostic tool is highly recommended.
2. Frequent monitoring of hepcidin hormone levels particularly in individuals with family history of IDA.
3. Launching of health education programs on anemia.
4. Conduction more hepcidin-oriented research especially for different age groups.

The Genetic Polymorphism of RhD among Blood Donors in Gaza Strip and its Reflection on Blood Transfusion Strategy

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ABSTRACT

Rh system is one of the most and highly complex blood group systems, as many as over 45 different Rh antigens have been serologically defined. The Rh antigens are expressed by proteins encoded by a pair of highly homologous genes located at chromosome 1. *RHCE* gene encodes CcEe antigens, while the *RHD* encodes the D antigen.

RhD is the most important, immunogenic and polymorphic Rh antigen from the clinical aspects (comprises at least 30 epitopes), which plays a key role in transfusion medicine. Anti-D antibodies remain the leading cause of the hemolytic disease of the newborn, and antigen D compatible transfusion is a standard practice in transfusion therapy. Partial D lacks one or more D epitopes, and the partial D individual could be immunized on exposure to normal D positive during blood transfusion or pregnancy. The DVI and DNB variants are the most frequent partial Ds that lack many of D epitopes, DVI is usually typed as D negative while DNB is typed as D positive.

We have examined 102 genomic DNA samples derived from blood donors expressing D positive and negative phenotypes, to detect DVI and DNB variants, and to investigate the molecular genetic of Rh negative phenotype. In addition 3 samples with discrepant RhD (weak D) were also investigated. To detect DVI variant; simplex PCR was used to detect the presence or absence of *RHD* exon 10/intron 4, while PCR-SSP was used to detect DNB variant. Of these, 3 DVI and 3 DNB samples were detected between blood donors. The PCR observations indicated a complete deletion of *RHD* gene in D negative specimens, and that the 3 weak samples were similar to normal *RHD* alleles but probably with weak *RHD* expression. A full concordance between phenotype and genotype was observed in D positive samples.

Key words: *Rh system, RhD, DVI, DNB, Anti D, Hybrid allele, PCR-SSP*

Conclusions and Recommendations

Conclusions

In our study, we can conclude the following:

1. The RhD positive/negative polymorphism is generated by the complete deletion of the RhD gene.
2. Many RhD antigens result from recombination events or point mutations generating different allelic forms of the *RHD* genes.
3. The results are consistent with our expectations, the most two frequent D variant alleles, DVI and DNB, are detectable among Palestinian blood donors.
4. The weak D allele is identical to normal *RHD* alleles, with respect to *RHD* intron 4/exon10 PCR assay.
5. The discordance between genotyping and phenotyping is confined only to DVI DNB and weak D phenotypes.
6. With D negative phenotypes, the use of two different regions in PCR assay minimized the risk of false negative results.
7. Such systematic knowledge could have considerable impact for typing and transfusion strategy in Palestine.
8. The selection of appropriate blood samples for studying the RhD alleles/variants at the molecular level must be taken into consideration.

Recommendations

According to our findings we strongly recommend the followings:

1. It is necessary to apply the RhD genotyping in clinical medicine. DNA typing will contribute to reducing the risk of alloimmunization, avoiding the common practice of wasting RhD negative blood units and minimizing the wastage of anti D prophylaxis.
2. Applications of RhD genotyping would be a useful tool when serotyping is not available, for example, in cases of massive transfusion and prenatal RhD typing of fetus at risk of HDN.
3. The rules that govern blood transfusion and blood donations strategies should be re-modulated to achieve the beneficial and maximum safety in the field of blood transfusion. For example, D negative transfusions is recommended if a recipient is known to carry DVI, DNB or any other partial D phenotype, and all potentially immunogenic donors should be recognized as D positive.
4. Parameters for anti Ds selection must be reviewed to meet the developed and current knowledge.s.
5. Further investigations of the genetic polymorphism and allelic diversity of RhD among Palestinian population, is strongly recommended. Other partial D alleles are difficult to discern by serologic means and need more investigations by genotyping approaches.
6. Finally blood transfusion is a critical practice requires that comprehensive policies and procedures for blood administration be designed, to prevent or reduce adverse

reactions. The development of these policies should be a collaborative effort among all personnel involved in blood administration. Policies and procedures must be accessible, periodically reviewed for appropriateness and monitored for compliance.

Expression of the multiple drug resistance associated genes: MRP1, LRP and BCRP among leukemia patients in Gaza strip.

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ABSTRACT

Hematological neoplasms are usually sensitive to chemotherapy, but with relatively high rate of relapse. Cell resistance to drugs is a major determinant of response to chemotherapy and its detection may be of clinical relevance. The role of expression of transmembrane carriers such as multidrug resistance related Protein 1 (MRP1), breast cancer resistance protein (BCRP) and lung resistance protein (LRP) genes in neoplastic cell survival and risk of relapse for leukemia patients was previously documented. Therefore, the aim of this study was to estimate the level of expression of MRP1, BCRP, and LRP genes in blood cells of leukemia patients in Gaza strip by quantitative real-time RT-PCR technique, and to investigate any correlation between the expression of these genes and other previous and current clinical findings of the patient.

Blood samples were collected from 70 leukemia patients (40 males and 30 females) admitted in the Hematology Departments of Al-Shefa hospital, the European Gaza Hospital and AL-Nasser pediatric hospital in Gaza strip. The specimens were collected during the period between May to November, 2009.

Patients' medical data were obtained from their records in the relevant hospitals, and included personal, medical, management and family information (e.g. age, type of disease, severity of case, date of diagnosis of disease, types, protocols of treatments, prognosis, previous tests results and others). A control group of 35 normal healthy individuals was included mainly to correct for any inter-individual expression difference as a result of gender and age variation.

This group was also used to compare the levels of gene expression in normal and leukemia patients. The level of expression of MRP1, LRP, and BCRP genes in cells of leukemia patients were quantitated by quantitative Real Time-PCR technique and normalized by the expression level of an endogenous control gene porphobilinogen deaminase (PBGD). The SPSS version 15 was used for statistical analysis.

Five types of leukemia, from different areas of Gaza strip, were included in this study. Thirty cases (42.9%) were acute lymphoblastic leukemia, 5 cases (7.1%) acute myeloblastic leukemia, 12 cases (17.1%) chronic lymphoblastic leukemia, 22 cases (31.4%) chronic myeloblastic leukemia and 1 case (1.4%) small lymphoblastic leukemia.

The mean age of cases was 32.9 ± 28.2 years and the mean age of controls was 27.2 ± 18.8 years.

MRP1 and LRP but not BCRP mean level of gene expression was significantly higher in leukemia group than normal control group. MRP1 gene expression in ALL patients was lower than all types of leukemia and significantly lower than in AML ($P=0.00$). LRP gene expression was significantly higher in AML and CML patients than in control group (AML: $P=0.021$ and CML: $P=0.001$). LRP gene expression in ALL patients were significantly lower than CML patients ($P=0.024$); and in CML patients higher than CLL patients ($P=0.046$). There was no statistically significant difference between leukemia types in BCRP gene expression levels. MRP1 and LRP mean levels of expression in remission was less than with no remission patients and this decrease of expression was statistically significant (MRP1: $P=0.003$ & LRP: $P=0.050$). The mean level of BCRP gene expression in remission patients was also less but with no statistical significance. When comparing the level of MRP1, LRP and BCRP according to management protocols and gender of patient no significant relationship was established.

The outcome of the current study indicates that higher levels of MRP1, LRP and BCRP expression are correlated with chemotherapeutic treatment failure of leukemia patients. Therefore we suggest these factors to be included in the design and application of chemotherapy protocols in Gaza Strip.

Key words: *Leukemia, Multidrug resistance, transmembrane protein, Real-Time PCR, Gaza Strip.*

Conclusions and Recommendations

Conclusions

1. The overexpression of MRP1 and/ or LRP genes, among others genes like MDR1 gene, may represent a hallmark of different leukemia types, particularly if managed by chemotherapy.
2. No matter what drug resistance associated gene is overexpressed, the leukemia neoplasm will have an increased risk of relapse and finishing of therapy as a result.
3. Extremely high levels of a particular drug resistance associated gene alone or in combination with others, may be lethal due to non-responsiveness to treatment and the resulting toxicity associated with the demand of proportionally increase drug doses.
4. If to be used for prediction of treatment outcome, one has to expand the number of genes tested to cover all possibly overexpressed ones.

Accordingly, a more comprehensive technique for testing, such as microarray technique, should be applied.

5.The proposed prognostic role of MRP1 and LRP in predicting chemotherapy outcome may be more profound in AML, CML and CLL patients but not ALL.

Recommendations

- 6.The decisive role of MDR genes in response of patient to chemotherapy should be taken in consideration when planning for management protocols.
- 7.Profiling of level of expression of such genes in different leukemia types should be done, in order to establish diagnostic guidelines and protocols.
- 8.More studies should be conducted in which other MDR targets are analyzed in leukemia as well as other malignancies.

Effect of antioxidant "taurine" addition on the reliability of complete blood count (CBC) and red cell indices of whole blood specimens stored at room temperature and at 4°C up to 7 days

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Abstract

Complete blood count (CBC) and its associated hematological indices are one of the most common and routine laboratory tests. The present study aimed at the evaluation of possible effects of adding antioxidant taurine on reliability and stability of complete blood count parameters and its related cell indices of whole blood stored *in vitro* at room temperature and 4°C refrigerator up to 7 days.

Random venous blood samples (20 ml each) were collected in K3-EDTA tubes from 25 apparently healthy nonsmoker male students. The collected blood was distributed almost equally into 2 sets of K3-EDTA tubes, each set of 4 tubes. One set of EDTA tubes was kept at the ambient room temperature (23 ± 2 °C) while the other set was kept at 4°C. For each temperature set, the four EDTA tubes correspond to:

control with zero taurine, 2.5 g/l taurine, 5 g/l taurine, and 10 g/l taurine concentrations. For each group, CBC analysis was performed at collection time and then daily for 7 successive days after collection and storage. Statistical comparisons of data were carried out using the paired t-test, and one-way analysis of variance (ANOVA). In addition, Mean Percentage changes were calculated and compared.

PLT count was significantly affected by storage temperature and time. Storage of EDTA blood with taurine at room temperature considerably enhanced the stability of PLT count over 7 days of storage, while taurine at 4°C showed no remarkable effect on the stability of PLT count. Neither storage temperature nor incubation with taurine at the different concentrations stabilize MPV of blood samples, with mean percentage change increased considerably per time and reached values of 25.4 and 28.1 % at room temperature and at 4°C, respectively on the 7th day.

RDW readings were stabilized with taurine addition at the different concentrations for 48 hours at room temperature, and for 72 hours with 5 g/l taurine at 4°C refrigerator.

RBC count showed instability over time at the different temperatures, while taurine at 10 g/l exerted some stabilizing effect on RBC at room temperature over the first 5 days of the storage period. The MCV readings were stable for 2 days both at room

temperature and at 4oC refrigerator, and taurine did not enhance the stability of MCV neither at room temperature nor at 4oC refrigerator. On the other hand, MCH readings were found to be unstable along the 7 days both at room temperature and at 4oC refrigerator, but addition of taurine to these samples exerted some stability on the MCH readings both at room temperature for 5 days and for 4 days at 4oC refrigerator. MCHC readings were unstable and exhibited a significantly decreasing trend with time despite of temperature or addition of taurine. Also, Hct values were unstable and exhibited an increasing pattern at room temperature and at 4oC refrigerator even in the presence of taurine. The values of Hb concentration showed stable values over the 7 days at both temperatures, with no advantage of taurine on the stability of Hb values. While WBC count revealed different stabilities at room temperature and at 4oC refrigerator which lasted for 7 days and 4 days respectively. However, at room temperature taurine at 5.0 and 10.0 g/l reduced the stability to 3 and 2 days, respectively.

It was concluded that: the different CBC parameters and its related indices exhibited variable stability patterns in terms of the storage temperature, the time period and the addition of taurine. Therefore, it is worthwhile for each laboratory to consider what conditions to be adopted when preserving EDTA blood according to what laboratory tests are of concern and intended to be performed.

Keywords: *Taurine, antioxidant, CBC, K3-EDTA, ANOVA and PLT.*

Conclusions

In conclusion, the different CBC parameters and its related indices exhibited variable stability patterns on the storage temperature, the time period and the storage with taurine. Some parameters and indices are more stable at room temperature than at 4oC refrigerator (WBC), others are stable at 4oC refrigerator than room temperature (RDW, RBC), others exhibited different levels of stability at the different temperatures (MCV, Hb) others are limited or unstable at any temperature over time (PLT, MPV, MCH, MCHC, Hct), in others the stability could be enhanced partially or totally by addition of taurine (PLT, RDW, MCH).

Recommendations

- 1.It is worthwhile for each laboratory to consider what conditions to be adopted when preserving EDTA blood according to what laboratory test are intended to be performed.
- 2.For PLT count, addition of taurine when preserving EDTA blood samples for 7 days at room temperature, is recommended.
- 3.For MPV, MCHC, and Hct, EDTA blood samples should be processed and measured within few (2-3) hours of collection.
- 4.For RDW, addition of taurine when preserving EDTA blood samples for 2 days at room temperature, and 3 days at 4oC refrigerator, is useful.

5. For RBC count, samples should be processed and measured within 2-3 hours of collection. In addition of 10g/l taurine may enhance RBC stability at room temperature
6. For MCV readings, samples should be processed and measured within 2 days of collection.
7. For MCH readings, samples should be processed and measured within 2-3 hours of collection. Alternatively, addition of taurine when samples are being processed and measured within 4-5 days, is recommended.
8. For Hb concentration, samples could be processed and measured within 7 days of collection.
9. For WBC count, samples should be processed and measured within 7 days at room temperature and within 4 days at 4°C refrigerator. Addition of Taurine should be taken into consideration because it reduces the WBC count stability at room temperature.

Identifying the Types of Bacteria in Out-Dated Platelet Concentrate Units from Al Shifa Hospital Blood Bank

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Abstract

Blood transfusion is one of the most dangerous therapy that could any doctor describe, because beside its great benefit it could have a chance for many transmittable life threatening agents like Human Immunodeficiency virus (HIV), Hepatitis-B virus (HBV), Hepatitis-C virus (HCV) and the one agent of our concern Bacteria, which may be related to post transfusion sepsis .Transfusion sepsis due to bacterial contamination of blood and blood components is serious problem compared to the great decrease in the incidence of transfusion of HIV, HBV and HCV, and this decrease come basically from the pre testing of blood and blood components for these transmittable agents. The most common blood components exposes to bacterial contamination is the Platelet Concentrate unit, because its unique storage conditions. Also it bears a big challenge because the golden way (Blood Culture) take almost longer time than the unit life shelf itself, that makes it unacceptable to be the pretesting method for platelet bacterial contamination (like in case of HIV, HBV and HCV).

As Al-Shifa hospital blood bank is the largest center that prepares, stores and transfuses platelet concentrate, so it was the target population to define the problem. one hundred and fifty units were collected after 6 days of preparation and tested by culture method; the positive isolates (n=7) were identified and their antimicrobial sensitivity against some antibiotics was tested. The isolates represent 4.6% of the total cultured 150 unit, distributed between these organisms: *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus* spp and *Escherichia coli* and they showed to be affected very well by all the tested antibiotics except for *Pseudomonas aeruginosa* which was resistant for all except the antibiotic Ciprofloxacin and *Escherichia coli* which was resistant to both Cefaclor and Trimethoprim.

According to these results, we recommend raising awareness among medical staff dealing with this problem despite their positions and effect in the working frame, because these findings need a high level of communication between the authorities

and the medical staff. Also this study recommends authorities to apply quality control standards in platelet preparation and storage

Key words: *Bacterial contamination, Post transfusion sepsis, platelet concentrate, Al-Shifa hospital blood bank, Gaza- Palestine.*

Conclusions and Recommendations

Conclusions:

Bacterial contamination of blood and blood components is a serious issue which attracts many countries to define it in their blood banks services, Al-Shifa hospital blood bank in Gaza facing these hazards, findings from this study may be summarized as follows:

1. The percentage of bacterial contaminated whole blood platelet concentrate units was 4.6%.
2. The isolated organisms were *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus spp*, and *Escherichia coli*.
3. The antimicrobial sensitivity test showed a wide range effect in almost all isolates except two isolates *Pseudomonas aeruginosa*, which was resistant to all tested antimicrobials except Ciprofloxacin as well as *Escherichia coli* which was resistant to trimethoprim and cefaclor.

Recommendations:

1. Improve donor skin disinfection (with iodine).
2. Asking about recent symptoms like diarrhea to exclude donor bacteremia.
3. In case of blood bags with diversion, the blood bank employer should use the diversion bag to discard the first 20 ml of donated blood and in case of double bags they should add the new transfer bag under high strict aseptic technique.
4. Perform visual inspection for platelet refraction, measure both glucose and PH level at day 0 and at the day of transfusion.
5. Apply a routine testing for microbiological quality of platelet concentrates.
6. Apply the rules of quality assurance.
7. Keep all units after 4 hours of transfusion in sterile plastic bags so in case the patient develops symptoms related to post transfusion sepsis, units could be tested for contamination.

Survival Analysis of Breast Cancer Patients in Gaza Strip

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Abstract

Survival analysis is concerned with modeling the time between entry to a study and subsequent events (such as death) for a group of subjects (such as patients of certain disease). Censored survival times occur if the event of interest does not occur for a patient during the study period .

In this thesis, survival analysis of breast cancer patients in the Gaza strip was conducted. Kaplan Meier model (KM) has been applied on data of breast cancer patients from the Gaza Strip in the period 2000-2005. The model provides very useful estimates of survival probabilities and graphical presentation of survival distribution. It is the most widely used model in survival data analysis. We describe in detail how to calculate the Kaplan- Meier estimates of the survivorship function before applying the model, as well as Confidence interval estimates for the survivorship function .

Moreover, the Log - Rank test will be a applied on breast cancer patients in the Gaza Strip to test whether two survival functions are equal. This is particularly useful in deciding upon which group of patients is more useful for these patients.

Finally, the well known Cox model that is a well - recognized statistical technique for exploring the relationship between the survival of a patient and several explanatory variables is also applied in this thesis on the same data set of breast cancer patients in the Gaza Strip.

When used to analyze the survival time for patients in a clinical trial, the model allows us to isolate the effects of treatments from the effects of other variables. The model can also be used a priori, if it is known that there are other variables besides treatment that influence patient survival and these variables cannot easily be controlled for in a clinical trial.

Conclusion

The Kaplan Meier method provides very useful estimates of survival probabilities and graphical presentation of survival distribution. It is the most widely used method in survival data analysis. We have been observed that the Kaplan-Meier estimation of

survivorship function (KME) $\hat{S}(t)$ has an inverse relationship with the variable time (t) .

For breast cancer data in the Gaza Strip, the mean survival time μ is estimated by 1751 days and the standard error of mean survival time is estimated by 62.512. The median survival time m for breast cancer cases in the Gaza Strip is approximately 2140 days at $\hat{S}(t) = 0.492$.

The estimated hazard function and graph hazard function (death rate) is generally high after the day 52, and rapidly increasing until the day 2140 from 0.0196 to 0.7091.

The estimated mean survival time μ_1 for the first group is 1583 days, the standard error of the mean survival time is 109.04, the estimated mean survival time μ_2 for the second group is 1832 and the standard error of the mean survival time is 74.23.

We have been observed that the first group and the second group are significantly different (KME) survival curves.

The second group, has better survival and better response to treatment than first group because the (KME) curve for the second group is consistently higher than the (KME) curve for the first group.

In other words the effect of treatment on the second group is greater than the effect of treatment on the first group to stay in remission and the hazard rate for the first group is higher than the second group.

We consider model 2 for the remission data. The fitted model written in terms of the Cox Proportional Hazard Model is given by.

$$h(t, \chi, B) = h_0(t) e^{-0.77 \text{ Groups age} - 1.04 \text{ surgery}}$$

A general formula for the adjusted survival curve for all covariates in the model is given by:

$$\hat{S}(t, \chi, B) = (\hat{S}_0(t))^{\exp(-0.77 \text{ Groups age} - 1.04 \text{ surgery})}$$

To obtain the adjusted survival curve, we then substitute the mean values in the formula in the model fitted. The formula and the resulting expression for the adjusted survival curve are shown below.

$$\hat{S}(t, \chi, B) = (\hat{S}_0(t))^{0.0377}$$

The recommendations

- 1- Applying the Kaplan-Meier Estimation of survivorship function (KME) $\hat{S}(t)$ and estimated mean survival time for all cancer patient with confidence interval for $\hat{S}(t)$.
- 2- The determination of the relationship between (KME) and time for all cancer patients and determination of the relationship between hazard ratio and time for all cancer patients, using the statistics program R.
- 3- A clinical oncologist may be interested in comparing the ability of two or more treatments to prolong life or maintain health for two group from patients ages . Almost invariably, survival times of the different groups vary. Therefore, we recommend using the Log.Rank Test For Comparison of two survival distributions for all cancer patients.
- 4- Using the Cox proportional hazards model (CPHM), for analyzing survival data , that contain the most important variables as predictors of survival time T , where T denotes days until going out of remission .death or survive., for all cancer patients in Palestine.
- 5- Reactivation and rehabilitation of the Cancer Registry Center in Palestine to know the exact oncology cases and its different diagnostic sources in order to define the problem and its spreading reasons .
- 6- It is important to develop the Cancer Patients data in cancer Registry Center . Furthermore , it is required to improve the cooperation between Ministry of Health and Palestinian Central Bureau of Statistics to minimize the gaps of indicators which depend on the Ministry of health data and estimated indicators of the PCBS which come as a result of health surveys .

Statistical Models to Analyze Survival Time for Lung Cancer Patients in the Gaza Strip

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Abstract

Cancer is a global disease and represents one of the biggest health problems as it has one of the highest prevalence rates and the highest cost of educational programs required on preventive measures, early detection and access to rehabilitation. Lung cancer is the most common causes of cancer mortality in the Gaza Strip. The aim of this thesis is to provide a model that is appropriate to predict survival time of lung cancer patients in the Gaza strip, and to identify risk factors on lung cancer mortality. Data on 181 patients with lung cancer was collected from the Cancer Registry in Shifa hospital - Gaza in the period 2005–2010. The patients had been followed up for a period of 6 years and the data involve some variables such as gender, age at diagnosis, residence address, smoking status and tumor grade. Exponential proportional hazards and Weibull proportional hazards regression were applied as parametric models with Cox regression and Akaike Information Criterion (AIC) was used to compare the efficiency of the models. Hazard ratio was used to interpret the risk of death to explore factors affecting the survival of patients. Multivariable analysis according to parametric and semi - parametric models showed that the smoking status and tumor grade of cancer increase the risk of death from cancer significantly.

The study concluded that the probability of death by lung cancer for grade 2 patients is more than those at grade 1. For smoking patients, the probability of death is more than that of nonsmokers. Based on AIC scores, the Weibull parametric proportional hazard model seems more appropriate for our data set, and we propose that the model should be used as a statistical model for the survival analysis of patients with lung cancer.

Conclusion and the Recommendations

Conclusion:

Survival analysis can be used to analyze data on the length of time it takes for a specific event to occur. A characteristic of “time to event” data is that we did not know the actual time to event for every person in our data set. We however, know this only for some individuals. This study was seeking to: (1) describe the pattern (distribution) of event times of the cohort under study; this was done using (KM), (2) to compare patterns of time to event across groups which was done using Log Rank Test and to explore the influences of possibly several factors on “time to event” which was achieved by Cox regression and parametric proportional hazard models (considering Weibull and exponential forms). Evaluation was also carried out on the models to establish which model is the most appropriate for the data. The (KM) method was used to estimate the survival time of lung cancer patients. The mortality rate was high in subjects who smoke and with tumor grade 2 (Figures 4.2 and 4.6). This claim was further authenticated by performing log rank test which produced similar results (Tables 4.5). Using Cox regression and (CPHM), covariates that significantly influence the survival of lung cancer patients were identified. Two covariates that are identified to affect the survival of the patients at 0.05 level of significant were smokers and tumor grade.

(AIC) was used to evaluate the performance of the models in analyzing the data. There was no major variability between the three parametric models as (Table 4.7). Among three models, the parametric model Weibull proportional hazards was the best model in multivariable analysis based on the value of the (AIC). The Weibull proportional hazards model (Table 4.7) appears to be an appropriate model according to AIC compared to other models. (CPHM) was fairly poor compared to other parametric models applied in this study.

The Recommendations:

1. We propose that the Weibull parametric proportional hazard model should be used in similar studies since it proved to be a useful statistical model for the survival analysis of patients with lung cancer.
2. The available data related of the lung cancer patient in Gaza strip shows that most of them was diagnosed in an advanced stage (IV). Furthermore, more than two third of them are diagnosed in such stage, as a result of that the effort should be gathered toward the early diagnosis and early detection of disease, Furthermore, health education is a vital policy that help in prevention of disease .
3. Smoking as all of us know, and proved by this research is one of the factor that my head to lung cancer and provoke its occurrence.
4. We do recommend the continuing development of the cancer registry systems in Gaza strip and assuring the quality of the system, which are and will help the research and researcher.