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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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PREVALENCE OF CLOPIDOGREL RESISTANCE AND GENETIC PROFILE AMONG A GROUP OF PCI PATIENTS IN DUHOK CITY

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Abstract.

Clopidogrel is a second generation thienopyridine that's used as a prophylactic anti-platelets following percutaneous coronary intervention (PCI) for patients with coronary heart disease. Not all patients who receive this medication show effective response as literatures have reviewed clopidogrel resistance as an issue on needs of further follow-up and study. The aim of this article was to assess clopidogrel resistance among a group of patients who underwent PCI. This study was conducted as a cross-sectional study during the period of one year. A total of 106 patients who underwent Primary PCI and were placed on clopidogrel for at least 7 days were assessed. Their blood sample was obtained and asses for platelets aggregation test. The mean age of the patients with CAD who underwent PCI was 58.5 between 31 and 80 years old. 68.9% of them were males and 31.1% were females. From the total 106 CAD patients, 70.5% of them responded to the Clopidogrel positively and 12.4% responded in a suboptimal way while 19 patients (17.1%) were clopidogrel resistant. No significant correlation were found between clopidogrel response and gender or age; P values respectively were 0.2324 and 0.4159. subsequently, genetic report was done for resistant cases and they showed no significant correlation with age (P = 0.8914) and gender (P = 0.2524). Clopidogrel resistance and poor response is of a significant value among patients and can be encountered. There was no correlation of clopidogrel to age or gender, yet further studies are indicated for the assessment of the genetic material and response profile.

Key words. Clopidogrel resistance, P2Y12, coronary heart disease, acute coronary syndrome, genetic profile.

Introduction.

Coronary heart disease (CHD) is one of the leading causes of morbidity and mortality world-wide and refers to a group of disease involving coronary arteries characterized by atherosclerotic plaque formation and subsequent ischemic events such as acute coronary syndrome (ACS) [1,2]. Its treatment depends on the clinical presentation of the patient and typically include controlling modifiable risk factors such as diet, hypertension, diabetes, exercise, and tobacco cessation [3]. Furthermore, it also requires the use of medication with adequate pain control, anticoagulants and anti-platelets with aspirin and clopidogrel [2,4].

Clopidogrel is a second generation thienopyridine that's used as one of the cornerstone medications for treatment of CHD, which acts by selectively and irreversibly blocking P2Y12 receptors on the platelets resulting in inhibition of platelets aggregation [5-7]. It has been approved that the treatment of cardiovascular and cerebrovascular accidents like unstable angina, NSTEMI, STEMI and strokes [8]. The medication is commonly prescribed as a dual antiplatelet therapy for patients with Post-ACS [9]. The dual-antiplatelet therapy (DAPT) has shown to decrease thrombotic events in patients with ACS [10,11]. Despite that there is a high individual variability in response to clopidogrel has been reported; poor response to range from 4 to 30% were reported [12]. Factors associated with clopidogrel resistance include obesity, diabetes and hyperuricemia [12]. Once the medication enters the body it undergoes enzymatic activation from the inactive prodrug, clopidogrel, to active metabolites [13]. This action takes place via variety of CYP enzymes such as CYP2C19 and CYP3A4 [14]. Genetic polymorphism plays a role in the matter of influencing the responses to clopidogrel most commonly involving CYP2C19 enzyme [15-17].

Clopidogrel in the active form can inhibit platelet aggregation for Thor lifetime (7 to 10 days), nevertheless, platelet function returns fully after 5 days from discontinuation of the treatment due to the turnover [18,19]. For patients undergoing PCI, poor response to clopidogrel has been regarded as an independent risk factor for major cardiovascular events [20,21]. This study aimed at assessing the rate of response to the Clopidogrel in patients with CAD who received the PCI and rate of mutation detection among Duhok population.

Patients and Methods.

This study was conducted as a cross-sectional study on a group of patients diagnosed as Acute Coronary Syndrome and underwent urgent Primary Percutaneous Coronary Intervention (PCI). A total number of 106 participants were enrolled (Figure 1). The study was conducted over a duration of one year. The process started with patients who underwent primary PCI and are placed on clopidogrel (Piax, Mylan, India) for at least one week at a dose of 75 mg taken at any time were followed up after for the process of blood sample collection for platelet aggregation test

They were categorized accordingly into 2 categories; responsive and resistance depending on the response to aggregation test. If the clopidogrel function test was normal, they continued with the schedule for one year. While those patients who were diagnosed as non-responders or partial responders for clopidogrel, they were sent to genetic testing which were further subdivided into homozygous, heterozygous for CYP2C19 gene mutations and no mutations.

Inclusion criteria; any patient who has underwent PCI and has received Clopidogrel for at least one week were included. All age groups and both genders were included.

Platelet aggregation test: blood samples were withdrawn from venous blood and platelet-rich plasma separated; the plasma samples were placed in an aggregometer. As the plasma samples were blended at room temperature, epinephrine was

added to enhance platelet activation. The samples become cloudy indicating platelets aggregation, the light transmission is recorded by spectrophotometer.

Genetic testing: PGX-CYP2C19 StripAssay (VienaLab Diagnostics GmbH, Austria) is a sequential in vitro steps that started with DNA isolated from a blood. The extracted DNA amplified by a polymerase chain reaction (PCR) for the target genetic regions using designed primers. The DNA products after amplification then hybridized to a test strip comprised immobilized, allele-specific probes for eight polymorphic loci (*2, *3, *4, *5, *6, *7, *8, and *17). Next, non-specifically bound DNA removed by washing, the specifically bound primer sequences were quantified calorimetrically using streptavidin-phosphatase and chromogenic substrates, forming in purple-colored bands on the strip. The formed band patterns correlated to genotype and predicted the phenotype—such as poor, intermediate, extensive, or ultrarapid metabolizer—to inform clinical dosing requested for drugs affected by CYP2C19 activity.

Statistical analyses: The general information of the patients was presented in mean SD) or no (%). The rate of response to the clopidogrel in patients with CAD who received the PCI and rate of mutation detection was determined in no (%). The association of response with the general information of the patients was examined in one-way ANOVA, independent t-test or Pearson Chi-squared tests. The significant level of difference was determined in a p-value of less than 0.05. The statistical calculations were performed in JMP Pro 14.3.

Results.

The age of CAD patients with underwent PCI was 58.5±10.2 years (ranged 31- 80). The participants were mainly males (68.6%). The 106 CAD patients who underwent PCI responds to clopidogrel variably, 70.5% of them responded to the clopidogrel positively, 12.4% responded in a suboptimal, remaining 19 patients (17.1%) responded negatively. Genetic testing 17.1% non-respondent, revealed that mutations were reported in 13 (68.4%) of these patients versus 31.6% with no mutation. The result of the clopidogrel monitoring test was 38.7±21 (ranged 2-105) (Table 1).

The total number of participants was 106 which all underwent testing for platelet aggregation. The results showed 19 with no response, 74 with response and 13 with sub-optimal responses (Table 2). Those with no response underwent genetic testing and showed no mutations in 6 and 13 with mutations (Table 3).

The study showed that there male and female patients and the patients with different age groups did not respond with a significant difference, but patients who did not respond to the clopidogrel received a higher dose of clopidogrel compared to those who responded or responded in a suboptimal way (Table 2).

The response to clopidogrel increased with ageing, since low response reported in young which do increase in older groups (Figure 2).

Regarding genetic mutation, the results confirmed that a non-significant differences (p=0.8914) existed between the age of participants with genetic mutations (55.3±11.1) compared to those without mutations (56.0±7.1) years. A non-significant differences (p = 0.2524) existed between non-responders female to clopidogrel (5 patients, 55.6%) with genetic mutations versus (4 patients, 44.4%) with no mutations. In male, (8, 80.0%) with mutations compared (2 patients, 20.0%) without mutations (Table 3 and Figure 3).

Table 1. *General information of the coronary artery disease patients underwent PCI.*

Characteristics (n=106)	**mean±SD**	**Range**
Age, years	58.5±10.2	31-80 years
Gender, no (%)	Female	33(31.1)
	Male	73(68.9)
Response	No response	19(17.9)
	Responded	74(69.8)
	Suboptimal response	13(12.3)
Genetic report	Detected	13(68.4)
	No detected	6(31.6)
Clopidogrel monitoring test	38.7±21	2-105

Table 2. *Contingency analysis of response by general characteristics.*

		Response to clopidogrel			
Characteristics (n=106)	**n(%)**	**No response**	**Responded**	**Suboptimal**	**p value**
Gender, n (%)	Female, (n=33)	9 (27)	20 (61)	4 (12)	0.2324b
	Male, (n=73)	10 (13.7)	54 (74)	9 (12.3)	
Age, mean (SD)		55.5 (9.8)	59.1 (10.8)	59.3 (7.0)	0.3791a
Age group, n (%)	30-39	1 (25.0)	3 (75.0)	0 (0.0)	0.4159b
	40-49	2 (18.2)	8 (72.7)	1 (9.1)	
	50-59	9 (25.0)	23 (63.9)	4 (11.1)	
	60-69	5 (13.2)	25 (65.8)	8 (21)	
	70-80	2 (11.8)	15 (88.2)	0 (0.0)	
One-way ANOVA and Pearson, b Chi-squared tests were performed for statistical analyses. Data expressed as frequency (%) and for each gender group or age ranges					

Table 3. *Associated factors with genetic mutations results in patients not respond to clopidogrel.*

Factors		Detected (n=13)	No detected (n=6)	p value
Age (years)	Mean (SD)	55.3 (11.1)	56 (7.1)	0.8914
Gender, n (%)	Female	5 (55.6)	4 (44.4)	0.2524
	Male	8 (80.0)	2 (20.0)	
Mean (SD) compared by independent t-test, no (%) compared by Pearson's Chi-squared test				

Table 4. *Distribution of the sample according to the allele of genetic mutations.*

Genetic mutations	Allele	n (%)
Homozygous		0(0.0)
Heterozygous		13(68.4)
	CYP2C19-2	7
	CYP2C19-8	1
	CYP2C19-3	1
	CYP2C19-17	4
No mutation		6(31.6)
Total		19(100)

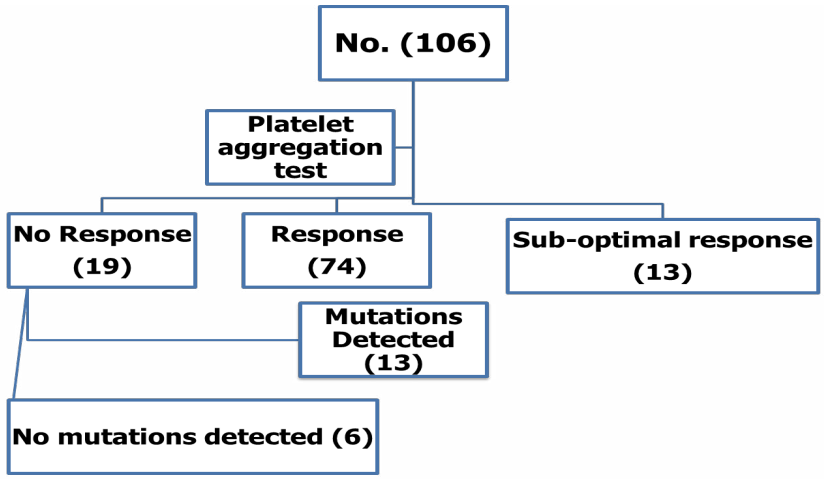

Figure 1. *Flow chart of enrolled patients and their resistance status for clopidogrel.*

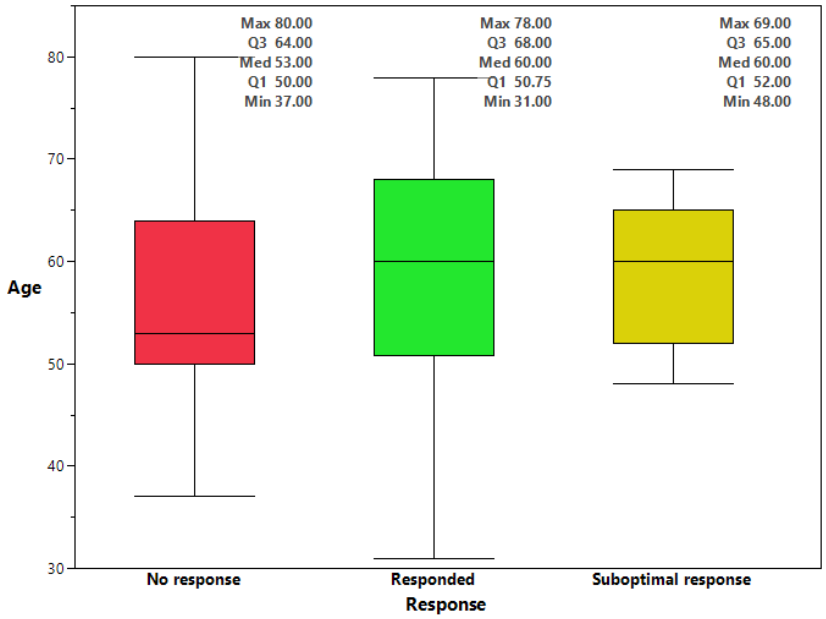

Figure 2. *Comparisons of age in patients with different response to Clopidogrel.*

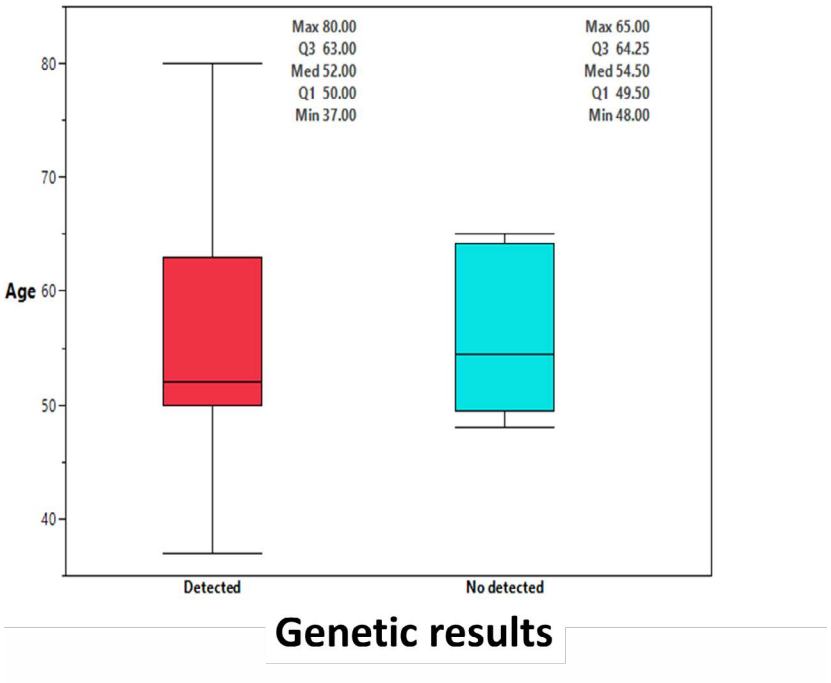

Figure 3. *Comparisons of age in patients with different genetic findings.*

The boxplot indicate that the detection of mutation is higher with more advanced age compare to younger age group, however, the results were more variable showing variation between individual (Figure 3).

The genetic results of 19 patients demonstrated that two-third (68.4%, n=13) were holding heterozygous mutations in the CYP2C19 gene, and none (0%) were homozygous. Nearly one-third (31.6%, n=6) of patients demonstrated no genetic mutations in the studied CYP2C19 alleles. In the heterozygous group of alleles, CYP2C19-2 and CYP2C19-17 were the commonest variant, 7 patients and 4 patients, respectively, when compared to CYP2C19-8 and CYP2C19-3 alleles shown in only 1 patient (Table 4).

Discussion.

Clopidogrel is approved antiplatelets used for patients with coronary heart disease, such as, ST-segment elevation myocardial infarction, and secondary prevention of ischemic heart diseases and stroke [8]. This medication works by irreversibly inhibiting platelet P2Y12 adenosine diphosphate receptor which prevents the downstream activation of the glycoprotein IIb/IIIa receptor complex therefore reducing platelet aggregation [21]. It requires enzymatic activation via several CYP enzymes including the CYP2C19 and CYP3A4 enzymes [22]. Any loss of function allele will not effectively metabolize clopidogrel leading to inability of inhibition of platelet activation [12,23]. It's recommended in higher doses as a loading dose, followed by a maintenance of 75 mg once daily to maintain its impact on platelet aggregation [22]. Around one third of patients on clopidogrel are characterized as poor responders to clopidogrel which increases the risk of thrombotic ischemic events [22]. The most likely factors that determines the likely response are the polymorphisms within the genes that regulate CYP2C19 activity and the related to polymorphisms of the ABCB1 gene [22]. This article is aimed at assessing the genetic response to clopidogrel among a group of patients.

Clopidogrel poor responders refer to the group of patients who failed to achieve and maintain an IPA after dosing. The platelet adenosine 5'-diphosphate (ADP) receptor P2Y12 (P2Y12R) plays a critical role in platelet aggregation, despite patients with ACS receive the primary management with PCI, they may still experience Major cardiovascular events that could be caused by clopidogrel resistance [24]. In this study, ~ 29.5% of the participants showed either no-response (17.1%) or Sub-optimal response (12.4%) indicating no significant benefit from the treatment. Additionally, among the non-responders, 68.4% of them revealed presence of genetic mutations in the CYP2C19 gene. A higher resistance rate (49.8%) was noticed by Giantini et al. [24]. Generally, Clopidogrel resistance among Asian population is much higher and estimated at 17.2-81.6% (6). The overall poor responders from the published articles range between 17-56% [23].

No significant difference was noticed regarding gender and age compared to the response and the dose of clopidogrel given. Indicating no difference in the dose and response. Contrary results were found with Hidayat et al., males were less likely to have clopidogrel resistance than female [25]. Additionally, females are more likely found to develop atherothrombotic events after 1-year follow-up of starting the treatment [26]. Additionally, among the non-responders, there was no difference between both genders and age regarding genetic report, indicating no influence of gender and age over the immunogenicity.

In our study we found that 68.4% of those with no response showed genetic mutations for CYP2C19*2,8,3 and 17 while 31.4% showed no mutations. Subsequently of them were lost in follow-up. CYP2C19 gene has been identified as the important

gene for activation of clopidogrel [27]. Clopidogrel resistance or non-functioning can led to certain negative impact on the individual, and this can be induced by several factors that interfere or impact the CYP2C19 gene function or action [23,25]. This can take place inform of mutations whether homozygous or heterozygous depending on the number of alleles affected or there will be no mutations but take place due to the impact of other factors such as other medications [28].

Nilotinib, a selective tyrosine kinases inhibitor used for treatment of cancer, has been found to competitively inhibit the metabolism of drugs that that are activated by several enzymes produced in the liver one of which is related to CYP2C19 [29]. Thus, one of our patients was on nilotinib which had no-response to clopidogrel and had negative genetic report.

Conclusion.

Clopidogrel is one of the important anti-platelets in DAPT for patients undergoing PCI. However, some individuals could present resistance to clopidogrel which are known as poor responders. This could be related to genetic material of some individuals yet the resistance was not associated with gender and age. The gender – gene interaction as well as age-gene interaction needs further studying and understating as it might impact clopidogrel drug metabolism inside the body. Further studies are required to assess the importance and risk factors of clopidogrel resistance. Any patient placed on clopidogrel, drug-drug interaction must be reviewed.

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Conflict of interest.

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