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Incidence of Chronic Myeloid Leukemia: Systematic Review and Meta-analysis

BY

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ABSTRACT

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Title: Incidence of Chronic Myeloid Leukemia: Systematic Review and Meta-analysis

Supervisor of Thesis: Ula, Middle Initial, Nur.

Background: To systematically assess and review the global incidence of Chronic Myeloid Leukemia using meta analyses and explore the factors associated with the variation of incidence of CML.

Methods: Observational studies reporting CML from the globe were systematically searched in databases including MEDLINE (Ovid) and ProQuest. The author screened the studies and extracted data and assessed the risk of bias. Hoy's risk of Bias tool was used to assess the biases in individual studies.

Results: Seven studies reporting CML Incidence were included. pooled estimate of the CML incidence were 0.92 per 100,000 populations (95% CI: 0.70 − 1.22), Subgroup analysis shows no significant regional variation between Europe vs other country and global estimate. There was no trend when CML plotted over time.

Conclusion: Given the pooled estimates vary widely with substantial heterogeneity, larger, well-designed studies especially in region and countries of developing world (Asia and Africa) are warranted to better understand the frequency and burden of CML.

DEDICATION

I dedicate this work to all cancer patients we encounter in our daily practice. It is our

responsibility to fight cancer and locate best evidence based into practice

.

ACKNOWLEDGMENTS

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Abbreviations:

SEER: Surveillance, Epidemiology, and End Results.

TKI: Tyrosine kinase inhibitor.

Ph: Philadelphia.

CP: Chronic phase.

AP: Accelerated Phase.

BC: Blast Crises.

AYA: Adolescents and young adults

AML: Acute Myeloid Leukemia

ALL: Acute lymphoblastic Leukemia

AP: Accelerated Phase

BP: Blast Phase

BCR-ABL: Break Cluster Region-Abelson

CBA: Chromosome Banding Analysis (karyotype)

CBC: Complete Blood Count

CCA: Clonal Chromosome Abnormalities

CCyR: Complete Cytogenetic Response

CHR: Complete Hematologic Response

CML: Chronic Myelogenous Leukemia

CP: Chronic Phase

CyR: Cytogenetic Response

DMR: Deep Molecular Response.

ELN: European Leukemia Net

EFS: Event-Free Survival

EUTOS: European Treatment And Outcome Study

FISH: Fluorescence In Situ Hybridization

IFNα: Interferon-α

HLA: Human Leukocyte Antigen

HSCT: Hematopoietic Stem Cell Transplant

IS: International Scale

MMR: Major Molecular Response

MR: Molecular Relapse

MRD: Minimal Residual Disease

NA: Not Applicable

PAOD: Peripheral Arterial Occlusive Disease

PFS: Progression-Free Survival

Q-RT-PCR: Quantitative Real-Time Polymerase Chain Reaction

TKI: Tyrosine Kinase Inhibitor

WHO: World Health Organization

Chapter 1: Introduction

1.1 Background

Chronic Myeloid Leukemia (CML) is a form of malignancy that affects the bone marrow and blood and characterized by high production of white cells named granulocytes [1]. these malignant cells (called blasts or leukemic blasts) slowly crowd the bone marrow and preventing the production non- malignant blood cell [1]. CML is associated with the fusion of two genes: BCR (on chromosome 22) and ABL1 (on chromosome 9) resulting in the BCR-ABL1(Break Cluster Region-Abelson) fusion gene. This abnormal fusion typically results from a reciprocal translocation between chromosomes 9 and 22, t (9;22) (q34; q11), that gives rise to an abnormal chromosome 22 called the Philadelphia (Ph) chromosome. It is this derivative chromosome 22 which harbors the BCR-ABL1 fusion gene [2]. figure 1.
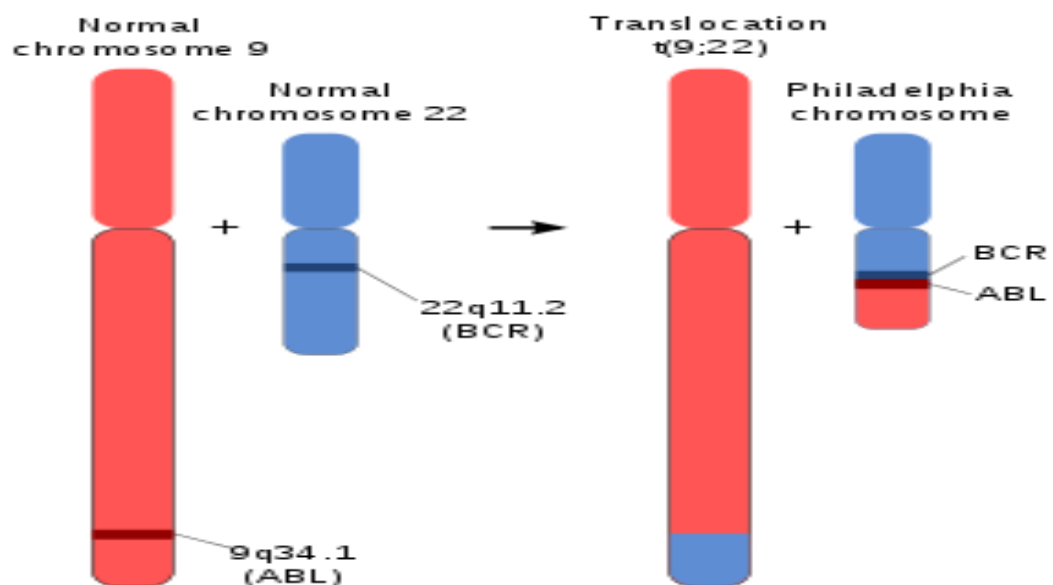

Figure 1. Normal chromosome vs translocated one.

CML patients are at increased risk of several Consequences and health problems; infectious complications, for example, are happening due to weakened immune system which may result in more severe complication [3]. Furthermore, some treatments used to manage CML can lead to infertility; Chang et al propose that Tyrosine Kinase Inhibiters(TKIs) passes the testis- blood barrier and decreases sperm thickness, sperm numbers, and movement [4]. The etiology of CML is largely unknown. The only deep-rooted predictor and risk factor is exposure to high doses of ionizing radiation, reported by Hsu WL et al in Japanese survivors following atomic attack in Hiroshima and Nagasaki [5].

Incidence of CML has been reported to vary widely between registries and countries. It is not clear if the global incidence is increasing and if certain populations are more affected than the others. However, Rohrbacher issued a study approximate CML incidence from 1 to 2 cases per 100 000 people every year [6]. Same study reported an example of France to show how CML prevalence changed over years and especially after introducing of Imatinib from 4.1% during 1998 to 2002 and of 9.3% during 2003 to 2007[7].

CML is more common in males than in females, it can happen in all age levels but is predominantly a disease of older population, accounting for 15% of all adult Leukemia's [6]. Although, it is commonly defined to take place in late adulthood, the median age varies among registries beginning the late 30's up to 65 years [8]. There is no solid evidence to suggest a particular ethnicity is more likely be affected, in spite of some reports of lower incidence rates in several Asian populations [9, 10].

CML treatment proceeded broadly after Imatinib was initially introduced in 1996 as a (TKI) with High specificity against BCR–ABL fused gene [11]. Consequently, CML survival rates have enhanced radically to provide a life

expectation near that of the Normal non-diseased population [12]. Alongside, its prevalence has increased in the last years and the necessity of nonstop TKI treatment in most cases is debatable and will have an influence on forthcoming healthcare related expenditure [10].

In order to cover the knowledge gap of Incidence variation over registries, and identify factors that may affect this variation. Our study aiming to assess systematically the global incidence of CML and quantify it and explain possible caused for variation based on time and geographical differences. Systematic Review and Meta-analysis was performed to locate all relevant studies that reported CML incidence under any time period and any population being studied. After collecting all studies, appropriate tool used to judge risk of bias and give consequent quality score. Then, estimations pooled and assessed for heterogeneity and publication bias.

1.2 Aims:

- To systematically review the global incidence of CML
- To quantify the global incidence of CML using meta analyses
- To explore the factors associated with the variation of incidence of CML.

Chapter 2: Literature Review

2.1 CML: Incidence, Prevalence and Burden

CML is a relatively rare disease as per WHO definition of rare diseases. The incidence of CML varies between different countries, populations and age groups. For instance, a recent, larger study form the USA reported an incidence of as high as 1.75 per 100,000 persons, while a Chinese study reported a somewhat lower incidence of 0.4 per 100 000 persons [14, 15]. According to the study "The global incidence and prevalence of chronic myeloid leukemia over the next ten years (2017-2027)", incidence of CML in Europe differ than other region with 1,4 100 000 persons and the prevalence, 11 cases per 100 000 persons in 2017[15]. CML is even rarer in children with an annual incidence of 0.06–0.12 per 100,000 children [16].

The fluctuation in rate continued to prevalence. For example, Visser et al. reported a prevalence of 5.6 per 100 000 persons in Europe in 2008 [17]. Approximately 70 000 persons, corresponding to 22.7 per 100 000 persons, suffer from CML in USA today which is expected to increase to 112 000 in 2020, 144 000 in 2030, 167 000 in 2040, and 181 000 in 2050, when it is expected to reach a plateau [18]. In Sweden, Ohm et al. have observed a prevalence of CML of 9.2 per 100 000 inhabitants in 2008, which is by 2050 expected to increase to 17 per 100 000 persons [19].

CML is also reported to have slight male dominance with a number of studies presenting males are more plausible affected than females. For instance, a recent Swedish study showed the male / female ratio of CML to be 1.2:1 [10]. Median age of the CML also appear to vary based on population and registries. More importantly population structure in the countries would also have an impact on this.

CML places a financial burden on patients that is associated with patients taking measures that may considerably affect quality of life and may adversely impact treatment outcomes. Quality of Life (QoL) in CML patient on long-term tyrosine kinase inhibitors therapy overall report QoL similar to that of the general population, the era of tyrosine kinase inhibitors has transformed CML from an often fatal disease to one with an excellent prognosis. The increasing burden is due to several factors, including population growth and ageing as well as the changing prevalence. With ongoing treatment, several patients living with CML may have to be able to cope with a substantial monetary burden associated with care, including medication payment and care expenditure, and other out of pocket costs [20].

2.2 CML: Management and Phases

CML was in the pre-TKI era a disease associated with poor prognosis and a short survival time, although a small number of younger patients were cured by bone marrow transplantation, the latter associated with considerable treatment related mortality and morbidity [21-22]. With the introduction of the TKI (Imatinib) in the early 2000s, the survival has rapidly increased and is currently pushing a 5-year relative and overall survival (OS) of nearly 90 % [23-24].

2.2.1 Treatment options:

Therapy choices for patients with chronic myeloid leukemia (CML) be determined by the stage of disease (chronic, accelerated, or blast phase), age at diagnosis, extra predictive features.

The introduction of Imatinib revolutionized CML treatment by inhibiting the BCR-ABL gene of the t (9;22) chromosomal translocation forming acute lymphocytic

leukemia and the Philadelphia chromosome characteristic of CMLs [25]. Imatinib is a first generation TKI that minimally inhibits BCR-ABL as compared to Dasatinib and Nilotinib. Imatinib also inhibits platelet-derived growth factor receptors at concentrations that are clinically relevant [26].

Fusing BCR and ABL creates a constitutive ABL tyrosine kinase that transforms hematopoietic progenitor cells. Imatinib was approved in 2002 to treat CML based on long-term efficacy, high molecular and cytogenetic response rates, and superior intolerability over therapies based on interferon [26].

Imatinib is a standard therapy for diagnosing CML in patients at the chronic phase and those who fail stem cell transplants or interferon therapies. Imatinib became a model for targeted cancer treatments [27]. Strategies for treating patients who resist Imatinib include dose escalation or adjusted pharmacokinetics using novel tyrosine kinase inhibitors.

Nilotinib and Dasatinib are used to treat patients who resist therapies such as Imatinib [10]. Nilotinib and Dasatinib were approved as clinically effective even though they exhibit differential safety profiles.

However, adherence to therapy, concomitant medications, dosing schedules for therapy, differential pharmacokinetic profiles, and mutation status should be considered in the decision-making processes.

2.2.1.2 Disease Phases:

CML is categorized into three groups that help predict the outlook of the disease. Different experts suggest different cut-offs for defining the phases, but the system of the World Health Organization is widely adopted [28].

2.2.1.2.1 Chronic phase

The bone marrow and blood of patients at the chronic phase has 10% blasts. The patients often exhibit mild symptoms that are easily treated using standard drugs [29]. Most diagnosis often occurs at the chronic phase.

2.2.1.2.2 Accelerated phase

The bone marrow and blood of patients at the accelerated phase have 15% blasts but no more than 30% [30]. Basophils account for 20% or more of their blood while the blasts make up approximately 30% of their blood. Low platelet counts not exceeding 100 x 1,000/mm3 and with no relation to treatment is evident [31]. Chromosomal changes in leukemia cells are also evident in patients with the Philadelphia chromosome.

2.2.1.2.3 Blast phase

The bone marrow and blood of patients at the blast phase have 20 % or more blasts. Large blast clusters are evident in the bone marrow, from which they spread to tissues and organs [32]. The phase acts like acute leukemia with most patients losing their weight and appetites and having fevers.

2.2.1.3 TKI Cessation:

CML treatment showed favorable result dramatically changed outcomes especially in patients in the chronic phase since the releasing of first and Second generation of TKIs in 2001and 2007 respectively [33]. Patients with this traditionally

lethal illness today experiencing survival similar to the general people [34]. Although it was firstly thought that TKI treatment must be persistent forever, it is nowadays well believed that a smaller group of patients who reach a deep and sustained molecular response (DMR) can efficaciously cease TKI therapy and sustain a treatment-free remission (TFR). This was primary proven in the STIM1 trial [35]. Termination of treatment in trial sites seems to not cause harm with the mainstream of patients who didn't succeed to keep a TFR retrieval a DMR after months of resuming TKIs. One patient only expired to date after converting to progressive phase disease among 2500 patients reported. The ununiformed trial standards and outcomes raises a number of obstacles to outline criteria for the suitable and safe time to halt TKI therapy in general practice.

Chapter 3: Methods: Systematic review and Meta-analysis

3.1 Prisma

The recommendations from the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) were used as a guide for reporting this systematic review and meta-analysis [36].

3.2 Inclusion Criteria

Eligible studies for this systematic review included the confirmed cases of CML in cohort or population-based studies of patients including case series and registry data. Both prospective and retrospective studies were included. Studies reporting the number, frequency or incidence of Chronic Myeloid Leukemia in any age along with appropriate denominator were included. Studies that reported any form of incidence like the crude one, age standardized or per person year will be included. In addition to studies that reported data on subgroups of patients were also included like CML with positive BCR/ABL or CML with negative BCR/ABL.

3.3 Exclusion Criteria

Randomized control trials (RCT), experimental studies, Cross sectional studies as well as the case-control studies assessing and studying CML were excluded, as they would not provide incidence data. Studies report CML as secondary to other type of cancer or if CML had transformed from other malignancy were also excluded as our focus is on primary CML incidence.

Studies that didn't report 95% confidence interval were excluded from quantitative analysis (Meta-analysis) but included in Qualitative assessment (Systematic Review) it is not possible to pool such studies in forest plot without CI.

3.4 Search Strategy

The search strategy was developed to include a comprehensive database search using broader search terms: chronic* OR chroniq* OR chronik* OR cronic* and myeloid* OR myelogen* OR myelitis* OR granulocytic* OR monocytic* OR myelocytic* and incidence OR epidemiology. Medical Subject Heading (MeSH) terms were used when appropriate using the above terms with a combination of 'and' and 'or' in accordance with search engine specifications.

3.5 Data bases

The databases searched were MEDLINE (Ovid), and ProQuest. Manual search was conducted looking for relevant studies reported in the reference lists of the included papers. The titles or abstracts of these publications were reviewed and duplicate entries were eliminated. The database search was performed in between 20th and 30th of February 2019.

3.6 Study Records

The extracted records were reviewed by the Author according to the inclusion and exclusion criteria. The duplicate records were eliminated and a PRISMA flow chart was created [36] (Fig 2)

3.7 Data Extraction

Data form the eligible studies were extracted by the author and collected on a master table. Name of the authors, year of publication, data on the time period covered by the study, location of the study, inclusion and exclusion criteria of the study, the reported population at risk, incidence or number of cases and size of

population at risk were collected. A qualitative narrative summary of the included studies was summarized in the result section.

3.8 Risk of Bias Assessment

All the included studies were assessed by the author for internal and external validity using the criteria for bias assessment in prevalence and incidence studies [37]. Figure 3. The assessment of bias was conducted for all the 25 papers included in the quantitative analysis. The result is reported in Table 1.

Risk of bias items	Risk of bias levels	Points scored
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	Yes (LOW RISK): The study's target population was a close representation of the national population.	0
	No (HIGH RISK): The study's target population was clearly NOT representative of the national population.	1
2. Was the sampling frame a true or close representation of the target population?	Yes (LOW RISK): The sampling frame was a true or close representation of the target population.	0
	No (HIGH RISK): The sampling frame was NOT a true or close representation of the target population.	1
3. Was some form of random selection used to select the sample, OR, was a census undertaken?	Yes (LOW RISK): A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling).	0
	No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	1
4. Was the likelihood of non-response bias minimal?	Yes (LOW RISK): The response rate for the study was ≥75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non- responders	0
	No (HIGH RISK): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders	1
5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes (LOW RISK): All data were collected directly from the subjects.	0
	No (HIGH RISK): In some instances, data were collected from a proxy.	1
6. Was an acceptable case definition used in the study?	Yes (LOW RISK): An acceptable case definition was used.	0
	No (HIGH RISK): An acceptable case definition was NOT used	1
7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes (LOW RISK): The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re- test, piloting, validation in a previous study, etc.	0
	No (HIGH RISK): The study instrument had NOT been shown to have reliability or validity (if this was necessary).	1
8. Was the same mode of data collection used for all subjects?	Yes (LOW RISK): The same mode of data collection was used for all subjects.	0
	No (HIGH RISK): The same mode of data collection was NOT used for all subjects.	1
9. Were the numerator(s) and denominato r(s) for the parameter of interest appropriate	Yes (LOW RISK): The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of low back pain).	0
	No (HIGH RISK): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	1
10. Summary on the overall risk of study bias	LOW RISK	0-3
	MODERATE RISK	4-6
	HIGH RISK	7-9

Figure 2. The 10 criteria used to assess bias in Table 2 (Hoy et al., 2012)

3.9 Data Synthesis

We pooled the quantitative data using Meta-XL version 5.3[38]. We reported the pooled incidence and 95% confidence intervals (CI) and explored the robustness of meta analyses using appropriate meta-analytical models based on the level of heterogeneity. Statistical heterogeneity was assessed using Cochrane Q statistic and I-squared Statistics.

Most prevalence and incidence meta-analyses encounter significant heterogeneity. The Random Effect Model (REM) is often recommended in the presence of significant heterogeneity between studies, including the Cochrane methods groups. In addition, the main analysis using REM models. Doi and Thalib argued that Quality Effect Model (QEM) were ideal when there is significant heterogeneity is encountered. However, unlike the random-effects model which depends on observed between-trial heterogeneity, the model suggests adjustment based on measured methodological heterogeneity between studies and propose a simple non-iterative procedure for computing the combined effect size [39].

Forest plots were used to display the incidence of CML with corresponding 95% confidence intervals. Doi's and funnel plot created by plotting the log event rate against the standard error were constructed to evaluate the publication bias.

3.10 Subgroup Analysis

As most of studies were performed on Europe and USA, Subgroup analysis by location was done by comparing incidence rates from Europe, USA and other countries studies with incidence Estimate from our study.

3.11 Incidence over time

In order to show and explain Incidence variability and see whether CML rates are changing over time. Estimates from each study has plotted against publication year as a proxy for data collection time.

3.12 CML and Age

Included studies has reported different median age from as low as 47 to as high as 72 years. In order to study whether CML Incidence increases as age increases, median age plotted against Incidence estimates.

3.13 Assessment of Heterogeneity

Heterogeneity in our study was assessed using the Cochrane Q statistics as well as Higgen's I^2 value. A p-value of <0.05 was considered significant for the Cochrane Q, and an $I^2 > 50\%$ was indicative of significant heterogeneity as per the Cochrane guidelines this study [40].

Forest plots were used to display the incidence of CML with corresponding 95% confidence intervals. Standard funnel plot created by plotting the log event rate against the standard error were constructed to evaluate the publication bias.

Chapter 4: Results

4.1. Search Findings flow chart

The total number of papers identified was 696. The flowchart below shows the procedure of processing the articles and identification of relevant publications.
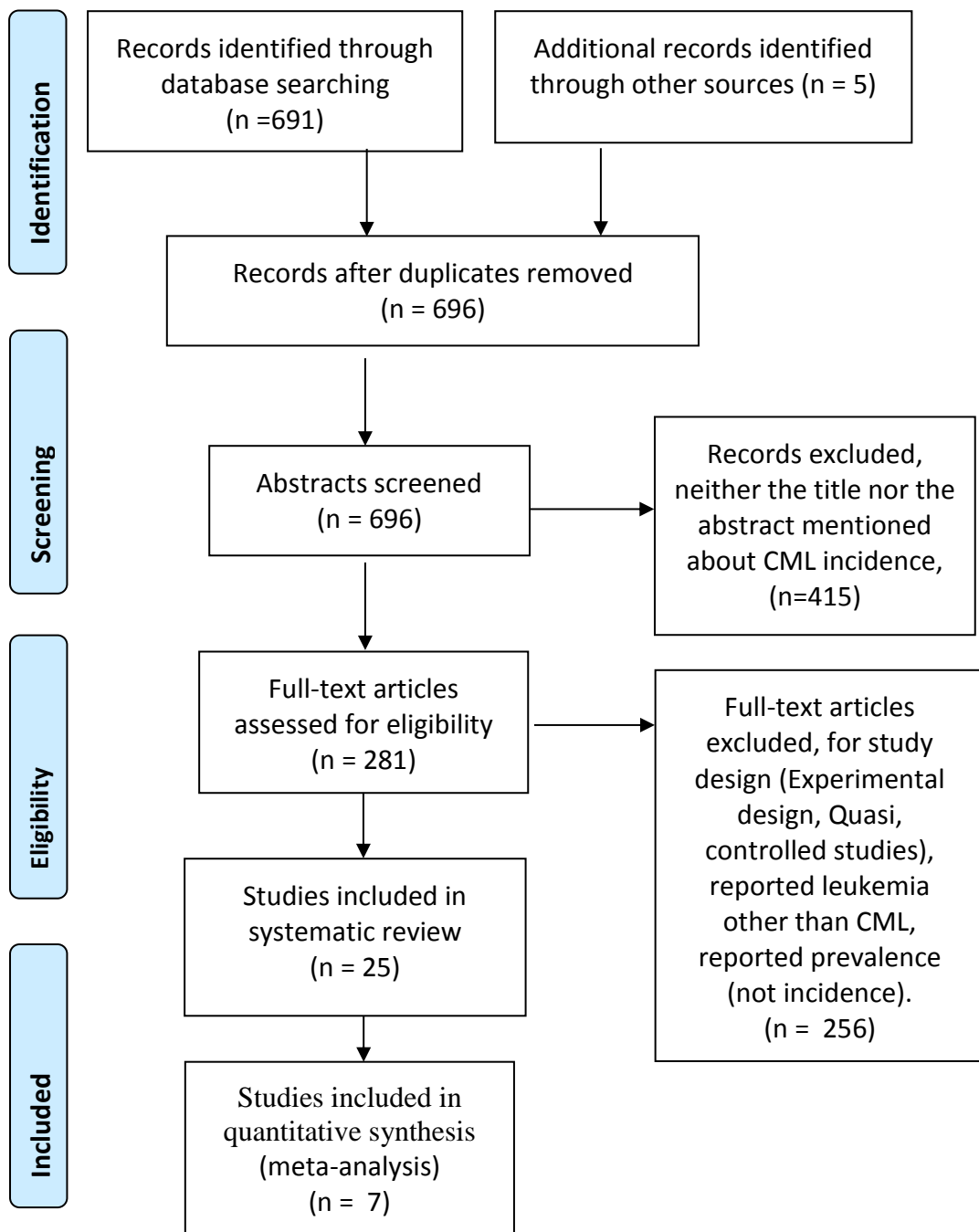

Figure 3: Systematic search strategy flow chart

4.2 Quality of the Studies

Of the 25 studies, 7 of them were rated to have high quality and 9 were of intermediate quality and remaining 9 were of low quality.

Table1. Assessment of bias per Hoy criteria described in figure 1.

Author \ Year	1	2	3	4	5	6	7	8	9	10	Score	Risk of bias
Al-Bahar et al 1993	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	7	Intermediate
Alston et al 2007	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	6	High
Beinortas et al 2016	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	9	low
Chen et al 2013	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	8	Intermediate
Fitzmaurice et al 2017	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	6	High
Harrison et al 2004	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	6	High
Hoffmann et al 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	9	low
Höglund et al 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10	Low
Hutchinson et al 2008	No	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	6	High
Jayasekara et al 2009	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	9	low
Maynadié et al 2010	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	7	Intermediate
McNally et al 1998	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8	Intermediate
Nakata et al 2017	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	6	High
Nguyen et al 2018	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9	low
Novak et al 2012	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	7	Intermediate
Oelofse et al 2018	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8	Intermediate
Osca-Gelis et al 2013	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8	Intermediate
Osorio et al 2016	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	8	Intermediate
Pheekoetal 2006	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	9	low
Sant et al 2010	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	9	low
Smith et al 2011	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	8	Intermediate
Thielen et al 2016	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	9	low
Troussard et al 2009	No	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	6	High
Visser et al 2012	Yes	Yes	Yes	No	Yes	No	No	No	Yes	Yes	6	High
Yamamoto et al 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	9	low

4.3 Study characteristics (Systematic Review)

A total of 25 studies were found to fit the selection criteria. Many studies were excluded due to inappropriate study designs (i.e., experimental, quasi, controlled studies). Studies reporting leukemia other than CML as well as studies reporting prevalence without incidence were excluded. Studies reported CML incidence without confidence intervals were only used in the narrative review and not for the meta analysis. This is because incidence was not possible to pooled without standard error or confidence intervals as they needed to be weighted appropriately.

Of the 25 studies that we included in this review, one study did not report the number of CML cases. Total number of new cases of CML diagnosed in these 24 studies were 118,292. Most of the studies covered a large geographical and populations but mainly were in North America and Europe. Two large studies were done in the United States covering a verity of states including: Detroit (Michigan), Atlanta (Georgia), Iowa, Utah, New Mexico, San Francisco-Oakland (California), Seattle Puget Sound (Washington) and Hawaii, covering more than 10% of USA population. Two large studies were reported from the Europe, covering more than 20 countries.

One study reported CML incidence from different parts of the world and included more than 60,000 cases of CML. The rest of studies were national or regional. These studies were analyzing CML cases occurring in Germany, Sweden, France (Burgundy), Spain (Girona), South - East England, UK, South Africa (Eastern Cape Province), Japan, Lithuania, Netherlands, Croatia, Australia, France (Basse-Normandie), Scotland, Kuwait and Canada (Alberta).

Many studies reported incidence based on population-based or national registries, the rest was depending on the laboratory data that were confirmed the CML

using BCR/ABL or bone marrow findings. The studies covered the duration of time ranging from 1975 to 2015, but the majority of studies were after 2000, post- TKI era. 16 studies had reported crude incidence per 100,000 populations, 14 studies had reported age standardized incidence per 100,000 standard populations, 8 studies reported both crude and standardized incidence and 4 studies reported person- year per 100,000. However only seven studies reported incidence with confidence interval that could be pooled using incidence meta-analysis.

Table 2. Summary of the 25 studies included in the systematic review.

Reference\ Year	Country	Period	No of cases	Median Age	Crude incidence	standardised incidence	Person-year	Reported Population
Al-Bahar et al 1993	Kuwiat	1979-1989	107	_	0.5	0.8	_	2.14 m
Alston et al 2007	Enngland	1979-2001	325	_	_	_	0.17	_
Beinortas et al 2016	Lithuania	2000-2013	601	62	1.28	0.87	_	3 m
Chen et al 2013	USA	1975 -2009	13,869	66	_	1.75	_	_
Fitzmaurice et al 2017	Global incidence	2015	64000	_	_	_	0.95	_
Harrison et al 2004	Scotland	1999-2000	64	_	0.64	_	_	5 M
Hoffman et al 2015	EUTOS (Europe)	2008–2012	2956	56	0.99	0.96	_	92.5
Höglund et al 2013	Sweden	2002–2010	779	60	0.9	_	_	9.5 m
Hutchinson et al 2008	Germany	1998–2000	218	57	0.79	_	_	9.2 m
Jayasekara et al 2009	Australia	1982-2004	1294	65	_	0.8	_	4.9 m
Maynadié et al 2010	(Burgundy, France)	1980-2004	141	56	0.9	_	_	512,272
McNally et al 1998	Uk	1984-1993	_	_	_	0.96	_	_
Nakata et al 2017	Japan	1993 -2010	53	_	_	1.1	_	_
Nguyen et al 2018	Alberta, Canada	2011 - 2015	_	48	0. 7	_	0.87	1.4 m
Novak et al 2012	Croatia	1988-2009	1122	_	_	0.68	_	4.4 m
Oelofse et al 2018	Eastern Cape Province - South Africa	2004 - 2013	154	47	0.24	0.34	_	6.5 m
Osca-Gelis et al 2013	Girona, Spain	1994-2008	102	62	1.15	0.96	_	731, 864
Osorio et al 2016	Spain	2010 - 2012	250	54	1.08	1.04	_	7.9 m
Pheekoetal 2006	South - East Eengland	1999-2000	180	65	1.72	1.1	_	5.5 m
Sant et al 2010	Europe (HAEMACARE project)	200-2002	2468	_	1.1	_	_	_
Smith et al 2011	UK	2004-2009	165	72	0.9	_	_	3.6 m
Thielen et al 2016	Netherlands	1989-2012	3585	62	_	_	0.85	_
Troussard et al 2009	Basse-Normandie - France	1997-2004	126	56	0.9	0.79	_	1.4 m
Visser et al 2012	Europe (PARECARE)	1995-2002	10047	_	1.2	_	_	497.5 m
Yamamoto et al 2007	USA	1997-2002.	15686	_	_	1.56	_	_

4.4 Pooled Estimates

The Random Effect Model was carried to pool the estimate **standardized incidence** and resulted in a pooled CML incidence of 1.10 per 100,000 standard populations (95% CI: 0.71 – 1.70) See figure 4. As expected, significant heterogeneity was encountered. The I^2 value = 98% and Q- value equals 171.48 with p <0.001.
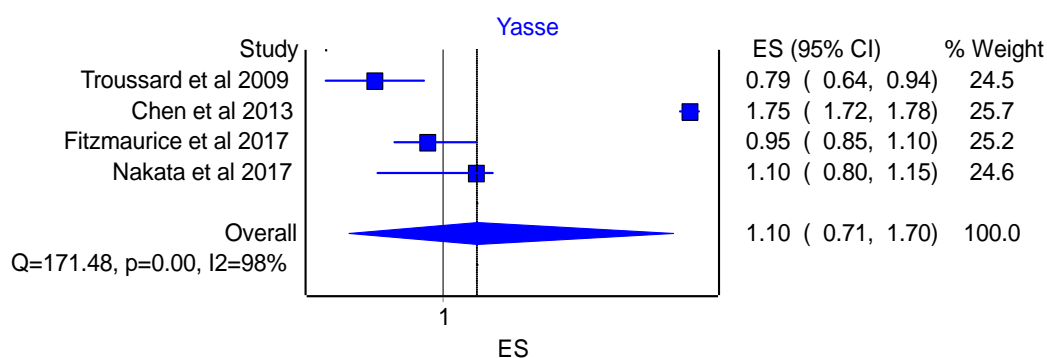

Figure 4: Forest plot of the age standardized incidence of CML under the Random-Effect Model.

Further, **Crude incidence** was also pooled using REM. The pooled estimate of the crude CML incidence was 0.72 per 100,000 populations (95% CI: 0.48 – 1.08) See figure 5. Again, significant heterogeneity was encountered as indicated by the I^2 value = 94% and p value of the Cochrane Q was <0.001.
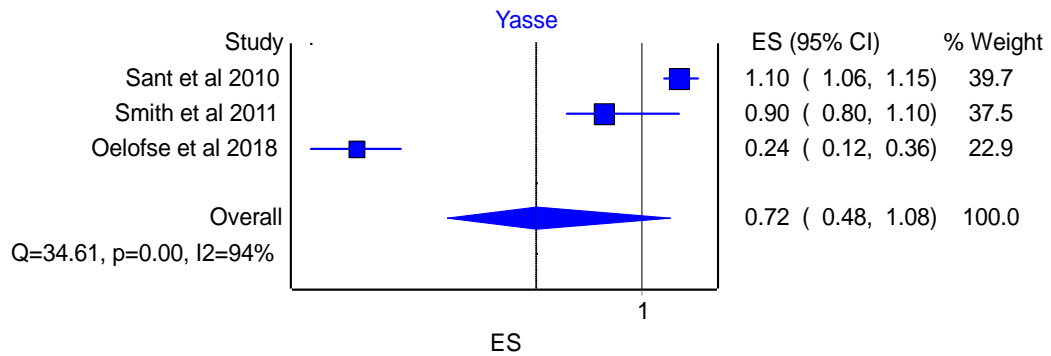
Figure 5: Forest plot of the Crude incidence of CML under the Random-Effect Model

We also carried a combined analysis including both crude and age standardized measures. We found the pooled estimate of the combined incidence were 0.92 per 100,000 populations (95% CI: 0.70 − 1.22). (See figure 6). We also used REM for these data synthesis and significant heterogeneity was indicated by an I^2 value of 99% and a P value of Cochrane Q to be $< 0,001$.
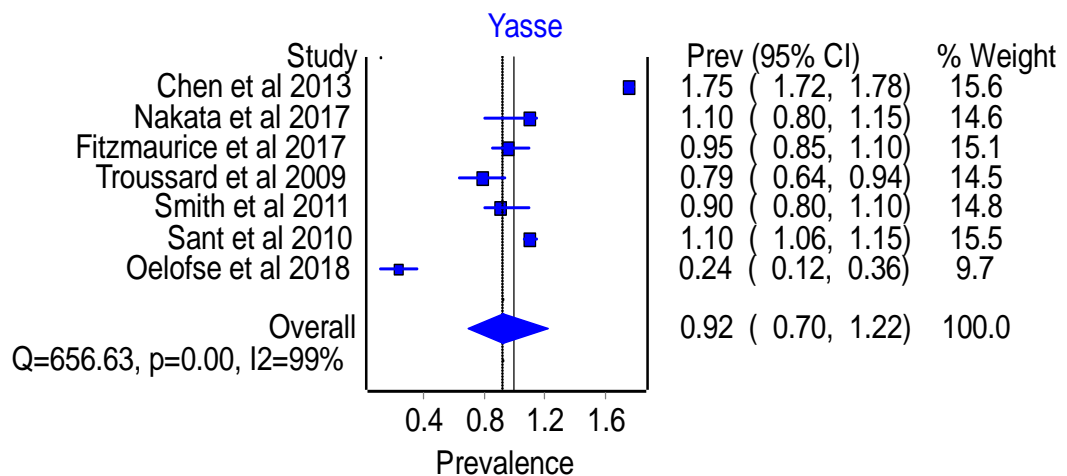

Figure 6: Forest plot of the incidence of CML under the Random-Effect Model

4.5 Publication bias

Although Hunter [41] argued classical funnel plots were not reliable for proportion measures. Funnel plot indicated that there appear to be publication bias (see Figure 7.). As the final number of included studies was reduced to be in total 7 studies (those who reprts confidence interval), Plot shows asymmetry to the left of plot which confirm the bias. In additin, LFK index shows a vlue of -7.88 which indicate major assymetry; this is also expected for the same reasons mentioned up.

Such puplication bias in the study can lead to misinterpretation of its results and may eventually lead to imprecise conclusions. In addition, can result in misleading conclusions and give the impression of unfounded precision of results.
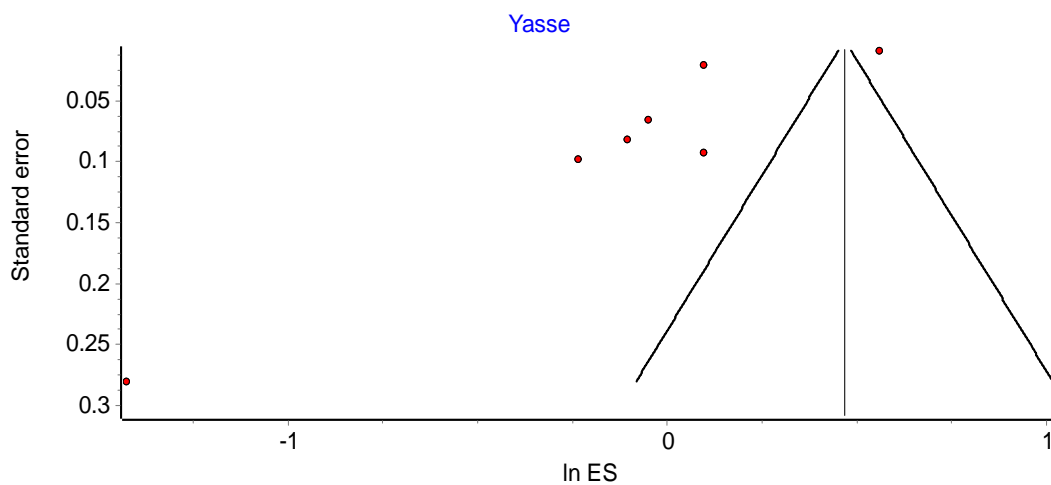

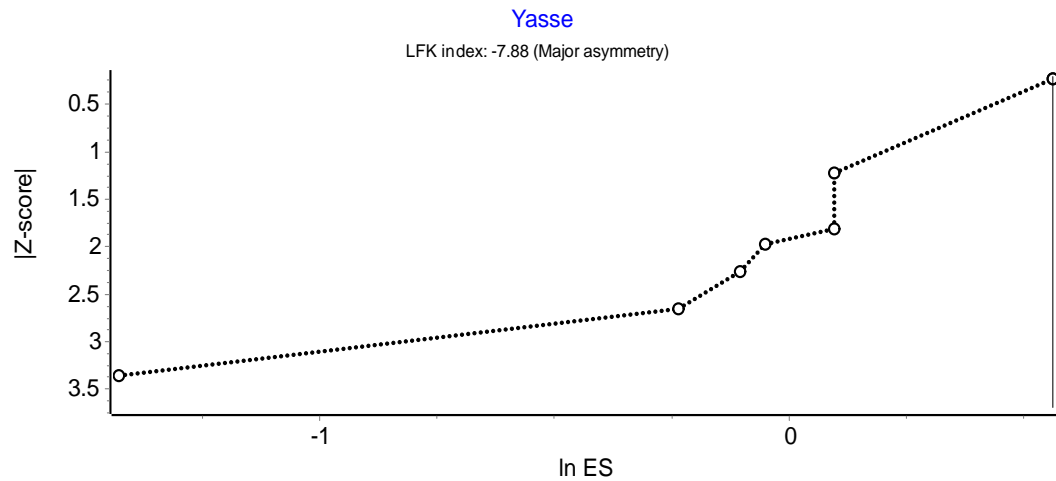Figure 7: Funnel Plot showing publication bias.

Figure 8: Doi Plot showing publication bias.

4.6 CML Variation

4.6.1 Regional Variation

USA and Europe were higher compared to our estimate from meta-analysis and other countries like Australia, Japan, Kuwait and South Africa.

Table 3: Subgroup analysis by region.

Region	Incidence
USA	1.65
Europe	1.07
All (Meta - analysis result)	0.92
Others	0.69

4.6.2 Time Variation

One of our objective of this study was to assess if the CML incidence are increasing over time as in line with most other cancer. We plotted the estimates from each study against the year of publication (proxy to data collection). As can be seen in the figure 9, there appear to be no trend of increase or decrease in the CML incidence with slope of 0.0037 which confirms of not changing incidence.
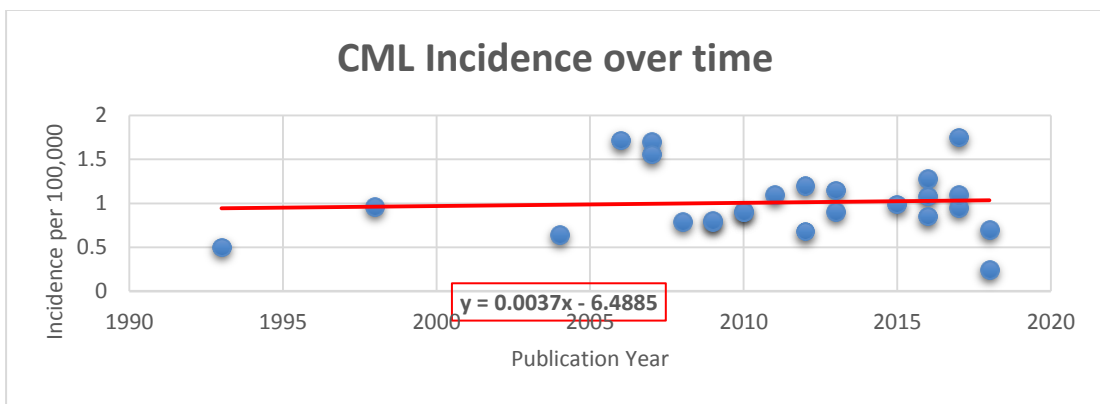

Figure 9: CML Incidence over time.

4.6.3 Age Variation

The lowest reported median age of patients diagnosed with CML was 47 years. the plot below (figure 10) shows linear trends and association between median age and CML Incidence.
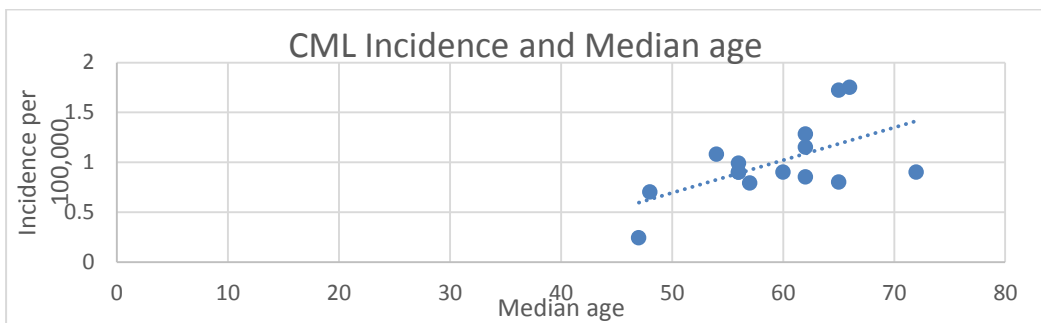

Figure 10: CML over median age.

Chapter 5: Discussion

This study included 25 eligible studies from different countries throughout the world to systematically review incidence in patients with Chronic Myeloid Leukemia. The study revealed that The pooled estimate of incidence of CML is 0.92 per 100,000 populations (95% CI: 0.70 – 1.22). Incidence rate estimate in our work are consistent with results from Sweden, England, Taiwan and EUTOS (European and Treatment, and Outcome study for CML) population based study that published CML incidence in 20 European countries [26, 42 - 44]. In contrast, the Surveillance, Epidemiology, and End Result (SEER) project in the Unites States reported higher incidence rate. Nevertheless, SEER project include patients without laboratory confirmation which may contribute to include more cases of CML and affecting the whole incidence rate [45]. The only study in middle east was in Kuwait within the period of 1979 and 1989 with incidence of 0.5 per 100000 populations [46].

The studies covered the duration of time ranging from 1975 to 2015 but the majority was after 2000. Studies included in the systematic review reported incidence in various ways, with crude, age-standardized and per person year.16 studies had reported crude incidence per 100,000 populations. Of them, 3 studies only entered the quantitative review and the rest didn't due to non-reporting confidence interval. The pooled estimate of crude incidence of CML is 0.72 per 100,000 populations (95% CI: 0.48 – 1.08).

14 studies had reported age standardized incidence per 100,000 standard populations. Of them 4 studies only entered the quantitative review and the rest didn't due to non-reporting confidence interval. The pooled estimate of crude incidence of CML is 1.10 per 100,000 standard populations (95% CI: 0.71 – 1.70). 8 studies

reported both crude and standardized incidence and 4 studies reported person- year per 100,000. In total, 7 studies reported incidence with confidence interval.

Subgroup analysis didn't show important regional variation between Europe and world estimate. While when others country (Japan and South Africa) compared to overall incidence shows some variation away from global incidence. The variation with Japan and south Africa shall be attributed to inclusion criteria of those studies which report incidence in all age group compared to European one that include patient above 18 years.

There was no trend of increasing incidence overtime and this can be attributed to study limitation described below. However, we expect more cases of CML next years as health technology has been improving compared to old methods which mean more accurate and early diagnosis. in addition, cancer in general - including CML is currently discovered and identified much earlier due to regular test and early detection program in asymptomatic individual.

Age is one of the factors associated with variation in incidence of CML. CML incidence increases by age, some of these variations are due to significant differences in the age distributions of the investigated populations. However, also age - standardized incidence vary considerably as well. So such differences cannot be explained solely by variances in the age. Methodological factors explain these discrepancies; In particular, the inclusion of patients with BCR-ABL-negative myeloproliferative disorders may account for the higher incidence of CML in some registries, such as SEER reporting an incidence of 1.75/100,000, varying from 1.4 to 2.0 between different regions within the USA.

The etiology of CML is essentially unknown. Ionizing radiation is the only established risk factor, having been linked to CML in atomic bomb survivors [5].

Results from a recent population-based case-control study suggested a weak association between smoking and CML, but this has not yet been confirmed by other studies [47]. In a study based on the Swedish Cancer Registry and Multigenerational Registry, Bjorkholm et al. found no significant familial aggregation of CML [48].

There is considerable heterogeneity in the estimates of the incidence of NEC across the studies included in the Meta-Analysis. This may be explained by the variability of the standard in health care systems, variability inclusion and exclusion criteria and differences in measurement methods.

Chapter 6: Limitation and Recommendation

6.1 Limitations

The meta-analysis study extraction was performed by one individual, the principle investigator. Most of studies were registry based that have a risk of many limitation; Cancer registries record cancer cases, not patients. Because a patient may have multiple primary cancers, the same person can appear more than once in a registry database. In addition, data might be delayed to be recorded causing less number of cases and thereby affecting numerators, denominators, and incidence rate. Furthermore, data based on registries not always representing the national cases especially in the case of big countries.

Apart from the conceptual issues about combining heterogeneous data, inadequate reporting of frequency estimates limited our study; In order to pool data, the Systematic Error (SE) or 95% CI for each estimate are required to weight the estimate. Only 7stufdies of studies reported SEs or 95% CI for their corresponding rates. We were not able to infer SEs for another of studies where exact data on the numerator, denominator and duration of recruitment were not fully available. As a consequence, pooled estimates for systematic reviews have to be based on the 'subset' of studies, which may introduce biases.

6.2 Recommendation

Although CML cases represent 15% of all leukemia and incidence is not increasing over time. Our study recommends to widely adopting programs that investigate patient routinely in primary health settings to early identify them and start targeted therapy treatment (TKI) as it proves high efficiency in treating CML. The synthesis of incidence data has been critical for the evaluation of disease burden measures such as the Disability-Adjusted Life Year (DALY), a metric increasingly relied on for the prioritization of health care and service planning (Murray et al., 1994).

In addition, Further research is needed to explore how much these variations in incidence are due to genetic susceptibility and/or environmental etiological factors. Future studies may also include cohort stratification by sociodemographic characteristics such as ethnicity or lifestyle factors, and consider other updated epidemiological measures.

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