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Machine Learning Approach to Identify Case-Control Studies on ApoE Gene Mutations Linked to Alzheimer's Disease in Italy

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Abstract: Background: An application of artificial intelligence is machine learning, which allows computer programs to learn and create data. Methods: In this work, we aimed to evaluate the performance of the MySLR machine learning platform, which implements the Latent Dirichlet Allocation (LDA) algorithm in the identification and screening of papers present in the literature that focus on mutations of the apolipoprotein E (ApoE) gene in Italian Alzheimer's Disease patients. Results: MySLR excludes duplicates and creates topics. MySLR was applied to analyze a set of 164 scientific publications. After duplicate removal, the results allowed us to identify 92 papers divided into two relevant topics characterizing the investigated research area. Topic 1 contains 70 papers, and topic 2 contains the remaining 22. Despite the current limitations, the available evidence suggests that articles containing studies on Italian Alzheimer's Disease (AD) patients were 65.22% (n = 60). Furthermore, the presence of papers about mutations, including single nucleotide polymorphisms (SNPs) ApoE gene, the primary genetic risk factor of AD, for the Italian population was 5.4% (n = 5). Conclusion: The results show that the machine learning platform helped to identify case-control studies on ApoE gene mutations, including SNPs, but not only conducted in Italy.

Keywords: machine learning; ApoE polymorphism; neurodegenerative disorders; Alzheimer's; ApoE; SNP; single nucleotide polymorphism; Italian; dementia; Italy

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1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia, accounting for approximately 60–80% of all dementia cases [1]. Numerous susceptibility genes and coding variants associated with the risk of developing AD have been identified so far [2,3]. The apolipoprotein E (ApoE) gene is the primary risk factor [4]. ApoE gene has three variant alleles (epsilon 2, epsilon 3, and epsilon 4), with differences in amino acid residues 112 and 158, which generate six genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4) and lead to three isoforms, E2, E3, E4 [4]. It is worth noting that ApoE is a 299-amino-acid glycoprotein with a molecular mass of ~34 kDa. Individuals possessing at least one copy of the ε4 allele in their genetic makeup are more susceptible to AD than those with ε3 [5]. Conversely, ε2 is suggested to have a protective effect [6]. Mutations, including Single Nucleotide Polymorphisms (SNPs) in the ApoE gene, were associated with the prevalence of AD [7–9]. SNPs on ApoE were linked to ethnicity [10]. Artificial intelligence (AI) represents a contemporary technological discipline dedicated to exploring and formulating hypotheses, strategies, technologies, and application systems aimed at emulating and expanding upon the facets of human intelligence [11]. Arthur Samuel coined the term "Machine Learning" in 1959 to refer to a set of algorithms and the development of classifiers.

The algorithm automatically learns from input data and constructs a model to anticipate new data [12] accurately. Today, with advances in artificial intelligence, machine learning is concerned with the development and application of computer algorithms that improve with experience [13]; traditionally, the management of extensive collections of paper has been organized and treated by topic using spreadsheets [14], dictionaries or supervised methods [15]; these types of approaches are very laborious and expensive and require good knowledge of the research field in which one wishes to operate. Thanks to the refinement of machine learning techniques, many of the steps in the literature review process have been simplified and automated, reducing workload for researchers and the time needed to evaluate the literature [16]. The digitization of healthcare data and the exponential spread of technology and new machine learning technologies are driving progress in the development and use of artificial intelligence in the healthcare sector [17,18]. AI is used to improve the precision medicine approach to treating neurodegeneration [19]. This work aimed to evaluate whether the MySLR platform based on machine learning can help extract scientific works focusing on SNPs on the ApoE gene in the Italian AD population.

2. Materials and Methods

A machine learning methodology was used to conduct a thorough analysis of a substantial volume of the scientific literature, extracting knowledge essential for the objectives of this research. While traditional algorithms are typically delineated for numerical and structured data, the content found in the scientific literature comprises unstructured documents, such as papers. To handle this unstructured textual data, the Latent Dirichlet Allocation (LDA) algorithm was selected to extend machine learning applications, particularly in extracting information from scientific journal articles [20]. The MySLR platform, using the LDA algorithm, emulates the behavior of "human-like intelligence" as accurately as possible. It can efficiently process substantial volumes of data, interpret texts, comprehend their content, extract necessary information, and reveal disguised connections among papers. This methodology involves establishing a model that individually identifies a set of "topics" (or themes) within texts, discerns the specific topic addressed by each, and subsequently recognizes the presence of these identified topics within various papers [21]. The platform is accessible at https://myslr.unical.it following registration (accessed on 10 November 2023).

2.1. Paper Location and Selection

We conducted specific research on three databases (Scopus, Web of Science, and Pubmed) to provide a comprehensive overview of scientific research concerning the presence of SNPs on the ApoE gene in the Italian population. The methodological approach involves three key steps: paper location and selection, paper analysis, and results presentation, aligning with the framework proposed by Denyer and Tranfield [22]. Three investigators (G.F.A.S, D.M.A.G., and E.C.) independently searched the PubMed, Scopus, and Web of Science databases to identify publications in peer-reviewed journals published before 10 November 2023. The search was conducted using the Boolean operators "AND" and "OR" to combine the following terms:("snps" OR "single nucleotide polymorphism" OR "Single-nucleotide polymorphism") AND ("ApoE" OR "apoliprotein E" AND ("Alzheimer disease" OR "alzheimer's disease" OR "AD" OR "LOAD") AND (italian OR italy)". By identifying primary topics within a collection of documents, topic modeling can generate succinct summaries that encapsulate the core content. The search conducted through Boolean operators allowed us to identify one hundred and sixty-four papers (n = 41 from Scopus, n = 61 from Web of Science, n = 62 from Pubmed), Figure 1. After duplicate removal assisted by the MySLR platform, ninety-two papers resulted from the three databases.

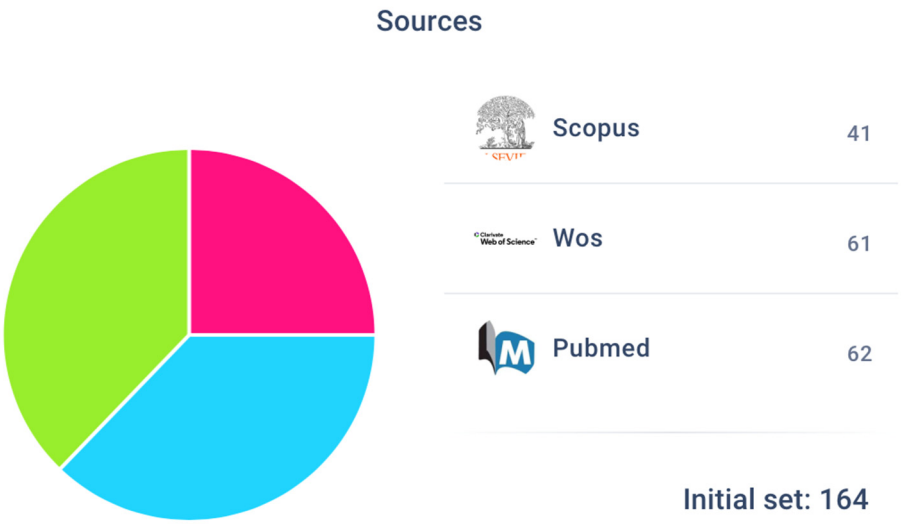

Figure 1. Pie chart produced by the MySLR platform, which describes the source of the papers, Scopus in fuchsia, Web of Science in blue, and Pubmed in green, before eliminating duplicates.

2.2. Paper Analysis

We applied a text-mining approach to the ultimate set of ninety-two papers to spotlight the primary research themes related to SNPs in the ApoE gene only in the Italian population. This approach relies on LDA, a statistical method that divides topics into each document. The model treats documents as probability distributions of topics and topics as distributions of words. In Natural Language Processing, a topic model is a statistical framework designed to identify abstract "topics" or themes within a collection of documents. These topics are not predetermined but are autonomously identified by the algorithm based on the frequency and occurrence of words in the texts. Leveraging such statistical principles, the employed algorithm identified two primary overarching topics (referred to as topics) linked to the keywords generated by the LDA procedure in the texts. It accurately assigned each text its corresponding semantic topic. The output of this procedure includes:

- *k* sets of relevant keywords (each set representing a topic).
- The document-term matrix depicts the statistical relationship between each paper and a specific topic (namely, the topic proportion).

This step aims to clearly articulate and explore the findings of the LDA procedure through an in-depth, human-based examination of significant papers clustered around the two identified topics. To assess the capability of the MySLR machine learning tool, we opted to retain all the papers retrieved using the specified search string. Following the recommendations of Blei [20], we set the value of k (number of topics to be extracted) to two. This choice resulted in a satisfactory topic coherence value (−1.15) [23], aligning with the ease of interpreting results for human readers. Topic coherence assesses the level of semantic similarity among highly scored words within a topic. This coefficient is a metric to gauge the quality of topic modeling, differentiating between semantically coherent arguments and mere statistical inference artifacts [24].

2.3. Results Presentation

The final stage of our methodological approach is explained in the "Results and Discussion" section. The objective at this stage is to provide a clear description and discuss the outcomes derived from the LDA procedure through a comprehensive human-based review of noteworthy papers clustered around the two identified topics by MySLR. The three steps of the machine learning process are illustrated in Figure 2.

Figure 2. Workflow of the machine learning approach via MySLR.

After these steps, with a dropdown menu, the MySLR allow us to identify studies classified as article, journal article, conference paper, proceeding paper, reviews. In our case, we did not find editorial articles, meta-analyses, letters to the editors, short communications, *erratum*, book chapters, notes, opinions, and personal comments, or retracted publications. Since our aim was to assess platform functionality, we did not exclude reviews from our tests. The flowchart, reported in Figure 3, depicts the selection algorithm.

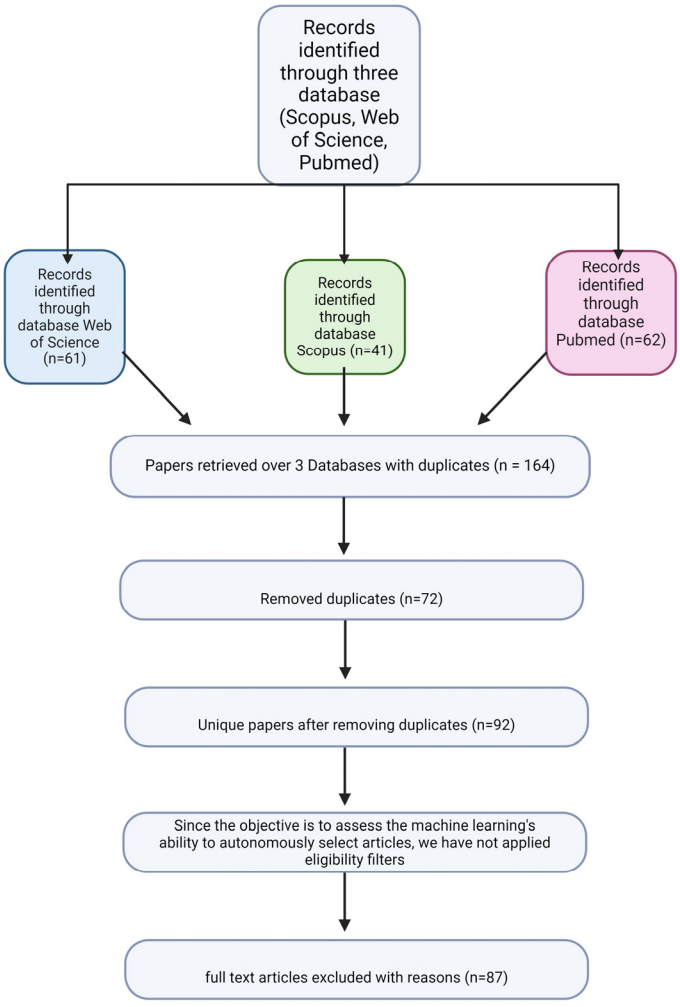

Figure 3. Flow diagram showing the algorithm of selection of eligible studies included.

3. Results

The initial literature search retrieved data from the MySLR platform, which loaded an overall published paper and ninety-two unique studies.

Utilizing the LDA procedure, we identified pertinent keywords linked to the two topics. Figure 4 illustrates the most significant keywords for each topic, visually represented through a "word cloud".

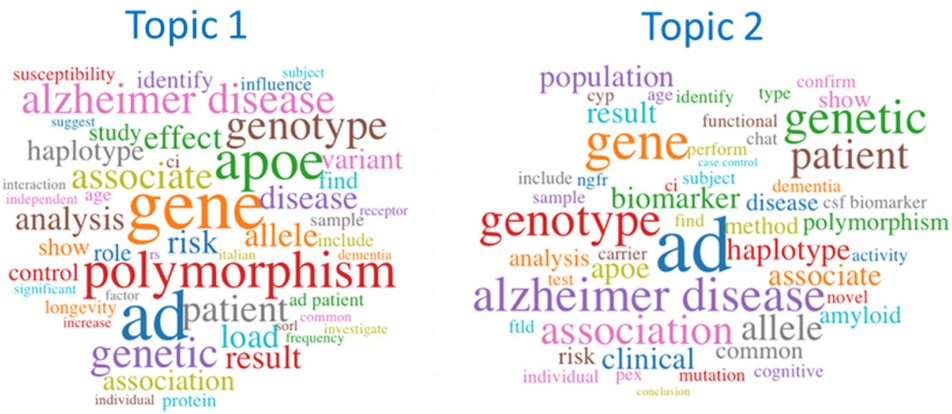

Figure 4. Word cloud highlighting the importance of the topic 1 and 2 keywords, adapted from the MySLR platform.

Topic 1 counts 70 papers and Topic 2 counts 22, as shown in Figure 5. From the analysis of the keywords, it was possible to identify the central theme of the two topics based on their relative weight. The weight of each keyword is calculated based on how often that keyword is repeated within the topic, also considering word associations. The MySLR platform can graph the final weight of the two topics (Figure 5), considering the weight of each keyword, the frequency with which the keyword is repeated, and the associations between keywords. Documents for topic one weigh 70,393, and documents for topic two weigh 21,607.

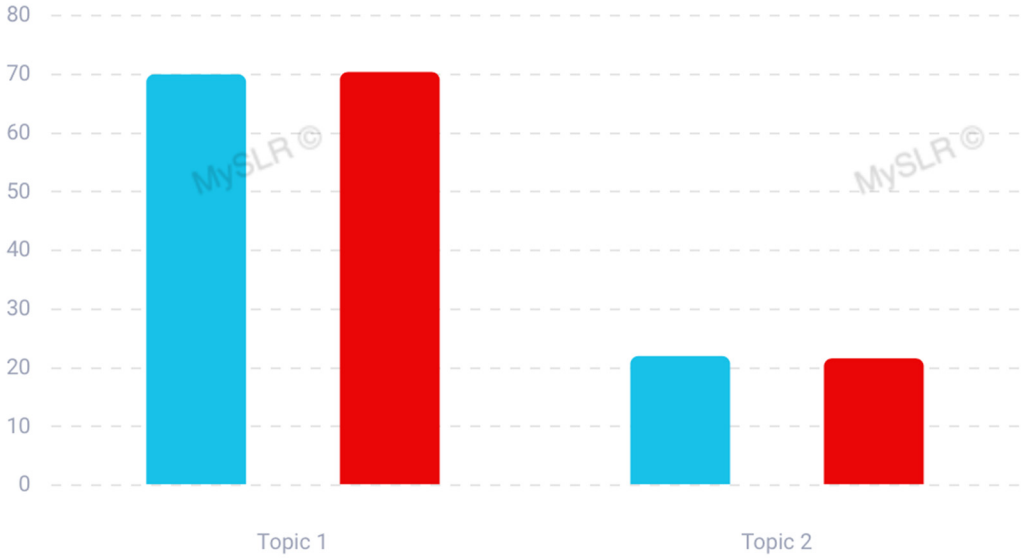

Figure 5. The blue column shows the number of documents for each topic by assigning the document to the topic that has the most weight in that document. The red one shows the number of documents for each topic by summing up the actual weight contribution of each topic to respective documents. Produced by MySLR platform.

The platform can produce a graph showing the number of articles published per year, as shown in Figure 6. Interest in the topic grew significantly from 2002 onwards, especially in 2008 and 2010.

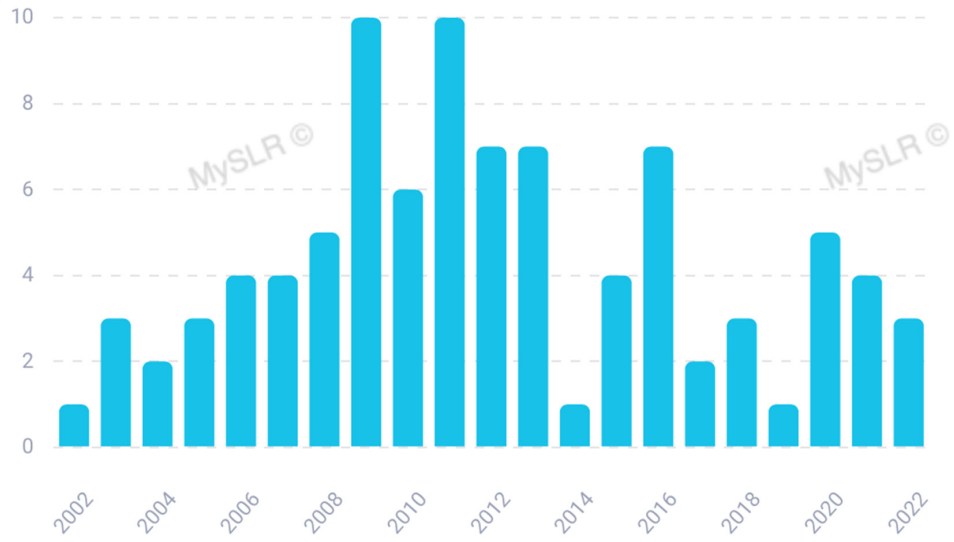

Figure 6. Papers publication over time. Produced by the MySLR platform.

Machine Learning also provides a way to show the trend of the topics over time. It also allows us to show the trend of topics over time. As shown in Figure 7, the interest in the two topics has a different trend over time: topic 1 generated much more interest in the scientific community, especially in the 2008–2010 period, where it reached the maximum interest. Even in 2016, interest was high, despite not exceeding the 2008–2010 threshold. For topic 2, the highest interest was reached in 2006 and 2012.

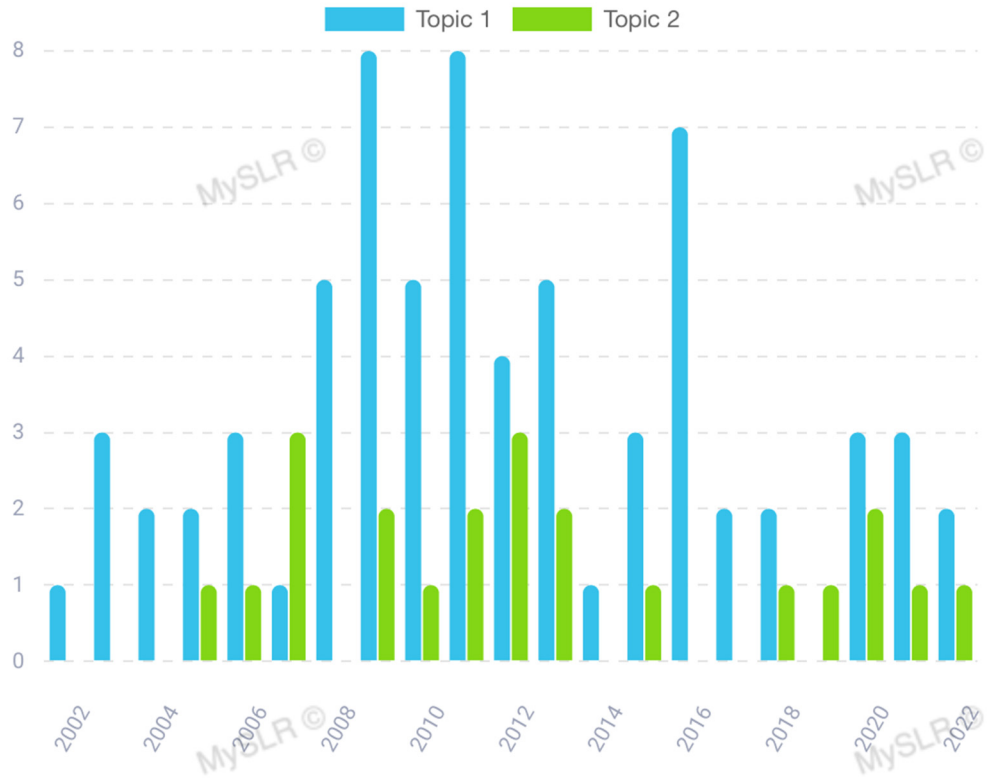

Figure 7. Topic papers over time. Produced by the MySLR platform.

3.1. Topic 1: Gene Polymorphisms Risk Factor for Alzheimer's Disease

Examining the top 30 most relevant terms and their frequency within papers grouped around the chosen topic, "load" (late-onset late-onset alzheimer's disease) reached the highest value (Figure 8). Analyzing the seventy papers clustered around this topic, it became apparent that the focal point of the topic was the influence of gene polymorphism on the progression and manifestation of AD, but not what we were searching for.

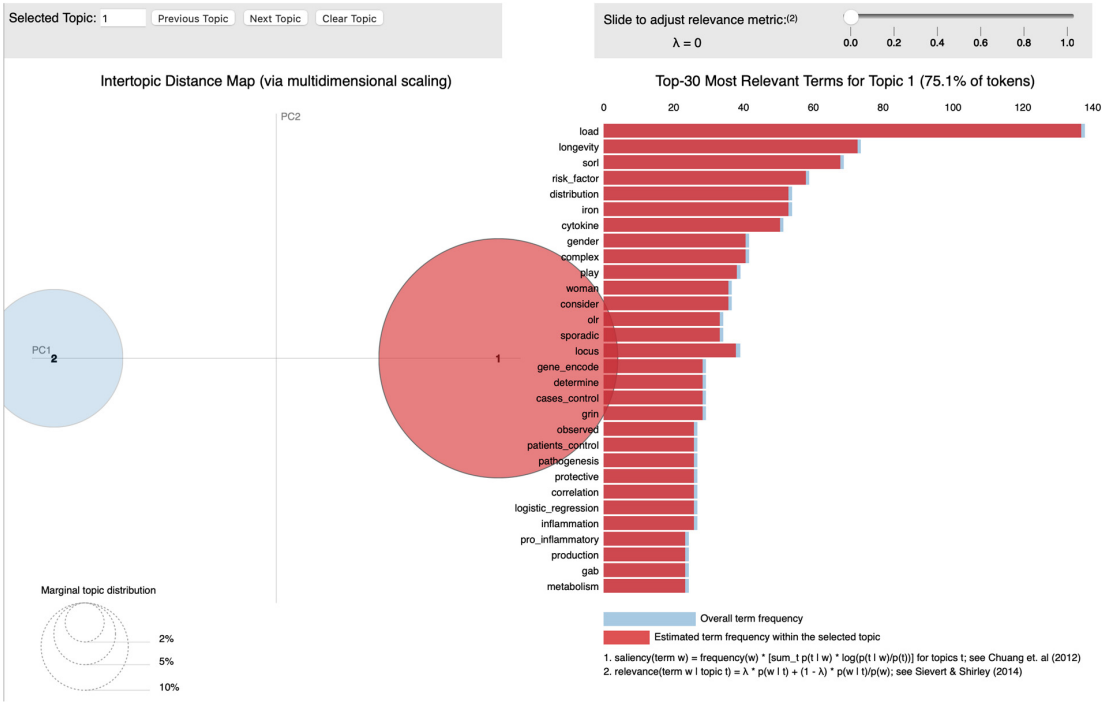

Figure 8. Inter-topic Distance Map related to topic 1. Circle 1 indicates topic 1, circle 2 is topic 2, extracted from the MySLR platform.

To gain insight into the papers generated by the machine learning algorithm under our query, we constructed a table delineating the main characteristics of each study, Table 1. Of the seventy papers in topic 1, 11.4% (n = 8) were not carried out in Italy, and we indicated it as "Not in Italy". The 1.4% (n = 1) were not carried only in Italy (in this case, we only considered the Italian population for studies that involved clustering the sample based on the state of origin. We left the wording "Not only in Italy" only for studies that did not include this clustering, while the studies that had the Italian population clustered were indicated as "Italy"); 2.85% (n = 2) were reviews or systematic reviews. Although there is a function to choose not to include it in the paper selection, we left it as such at this stage. The 8.57% (n = 6) were not considered as they were not conducted in Alzheimer's patients and therefore did not answer the search query. It is worth to mention here that AD is the most frequent type of dementia associated with genetic mutations [25,26].

Table 1. Overview of the characteristics of the papers included by machine learning in topic one.

Name, Year	Ref	Gene	Mutations	Localization	Other
Albani et al., 2012	[27]	----------	----------	----------	Not in Alzheimer
Andreoli et al., 2014	[28]	GRINB2	rs7301328 (GRINB2), rs1805482 (GRINB2), rs3026160 (GRINB2), rs1806201 (GRINB2), rs1806191 (GRINB2)	Italy	Alzheimer

Table 1. *Cont.*

Name, Year	Ref	Gene	Mutations	Localization	Other
Bagnoli et al., 2007	[29]	IL-10	rs1800896 (IL-10), rs1800871 (IL-10)	Italy	Alzheimer
Bagnoli et al., 2013	[30]	TOMM40	rs157580 (TOMM40), rs2075650 (TOMM40), rs15758 (TOMM40)	Italy	Alzheimer
Bartoletti-Stella et al., 2022	[31]	ELAVL1, EP300, EPHA1, FERMT2, INPP5D, MARK2, MARK4, PICALM PLCG2, PTK2B, RIN3, TOMM40 ZCWPW1, ADAM10, BIN1, CLU, CR1	c.112A > G (ADAM10), c.556dupC (ADAM10), c.696C > A (BIN1), c.865G > A (BIN1), c.1462-3C > T (BIN1), c.509C > T (CLU), c.4956G > A (CR1), c.4356T > C (CR1), c.765C > T (ELAVL1), c.2194C > T (EP300), c.928A > G (EPHA1), c.1077G > C (FERMT2), c.1538C > T (FERMT2), c.470G > A (INPP5D), c.2085C > T (INPP5D), c.1611C > T (MARK2), c.1553C > T (MARK4), c.1231G > C (PICALM), c.3379C > A (PLGC2), c.408G > A (PLCG2), c.2591C > T (PTK2B), c.2377T > C (RIN3),c.384C > G (TOMM40), c.1834C > T (ZCWPW1), c.314A > G (ZCWPW1), c.283-5T > G (ZCWPW1)	Italy	Alzheimer
Belloy et al., 2022	[32]	ApoE	rs439401 (ApoE)	Not in Italy	Alzheimer
Bizzarro et al., 2009	[33]	**ApoE**	**rs449647 (ApoE), rs405509 (ApoE), rs769446 (ApoE), rs429358 (ApoE) rs7412 (ApoE)**	**Italy**	**Alzheimer**
Bosco et al., 2013	[34]	----------	----------	----------	Review
Broer et al., 2015	[35]	----------	----------	----------	Not Alzheimer
Bucossi et al., 2012	[36]	ATP7B	rs1061472 (ATP7B), rs732774 (ATP7B)	Italy	Alzheimer
Capurso et al., 2010	[37]	IL-6	–174 G/C (IL-6)	Italy	Alzheimer
Capurso et al., 2010	[38]	**GSTO1, APOE**	**rs7412 (ApoE), rs429358 (ApoE),** rs4925 (GSTO1), rs1804834 (GSTO1)	**Italy**	Alzheimer
Cellini et al., 2009	[39]	SORL1	rs661057 (SORL1), rs11218304 (SORL1), rs560573 (SORL1), rs12364988 (SORL1), rs668387 (SORL1), rs689021 (SORL1), rs641120 (SORL1), rs556349 (SORL1), rs2070045 (SORL1), rs1699102 (SORL1), rs3824968 (SORL1), rs2282649 (SORL1), rs1010159 (SORL1)	Italy	Alzheimer
Ciminelli et al., 2020	[40]	AKR7A2, ALDH5A1, ABAT	rs4646832 (ALDH5A1), rs4646828 (ALDH5A1), rs2760118 (ALDH5A1), rs3765310 (ALDH5A1), rs1043657 (AKR7A2), rs1731017 (ABAT)	Italy	Alzheimer
Clarelli et al., 2016	[41]	CHRNA7	rs6494223 (CHRNA7), rs8024987 (CHRNA7)	Italy	Alzheimer
Colacicco et al.,2009	[42]	A2M, ORL1	rs669 (A2M), +1073 (ORL1) +1071 (ORL1)	Italy	Alzheimer

Table 1. *Cont.*

Name, Year	Ref	Gene	Mutations	Localization	Other
Corbo et al.,2009	[43]	CYP19	rs12907866 (CYP19), rs17601241 (CYP19), rs4646 (CYP19)	Italy	Alzheimer
Cruz-Sanabria et al., 2021	[44]	----------	----------	----------	Not Alzheimer
DeMichele-Sweet et al., 2021	[45]	ENPP6, SUMF1	rs9994623 (ENPP6), rs201109606 (SUMF1)	Not in Italy	Alzheimer
Di Maria et al., 2012	[46]	NGF	rs6330 (NGF), rs11466110 (NGF), rs11466111 (NGF), rs6325 (NGF), rs35941329 (NGF)	Italy	Alzheimer
Emanuele et al., 2011	[47]	CDKN2B-AS1	rs1333049 (CDKN2B-AS1)	Italy	Alzheimer
Finckh et al., 2003	[48]	PLAU	−141 C/T (PLAU)	Italy	Alzheimer
Fortney et al., 2015	[49]	----------	----------	----------	Not alzheimer
Galimberti et al., 2008	[50]	NOS 1	Ex1f-VNTR (NOS1)	Italy	Alzheimer
Guerini et al., 2016	[51]	SNAP-25	rs363050 (SNAP-25), rs363039 (SNAP-25), rs363043 (SNAP-25)	Italy	Alzheimer
Hollingworth et al., 2011	[52]	CUX2, CDK1, CNTN5, C16orf88, IQCK, MS4A6A, CR1, MS4A6A, BIN1, ABCA7	rs3764650 (ABCA7), rs744373 (BIN1), rs670139 (MS4A4E), rs3818361 (CR1), rs610932 (MS4A6A), rs7191155 (IQCK), rs4782279 (IQCK), rs1858973 (IQCK), rs739565 (C16orf88), rs10501927 (CNTN5), Rs10761558 (CDK1), rs3809278 (CUX2)	Italy	Alzheimer
Jun et al., 2016	[53]	ARL17B	rs2732703 (ARL17B)	NR	Alzheimer
Lambert et al., 2009	[54]	CLU, CR1	rs11136000 (CLU), rs2279590 (CLU), rs9331888 (CLU), rs6656401 (CR1), rs3818361 (CR1)	Italy	Alzheimer
Lambert et al., 2013	[55]	BIN1, HLA-DRB5/HLA-DRB1, ZCWPW1, PTK2B, CELF1, MS4A6A	rs6733839 (BIN1), rs9271192 (HLA-DRB5/HLA-DRB1), rs1476679 (ZCWPW1), rs28834970 (PTK2B), rs9331896 (CLU), rs10838725 (CELF1), rs983392 (MS4A6A)	Italy	Alzheimer
Lanni et al., 2012	[56]	COMT	rs4680 (COMT)	Italy	Alzheimer
Laws et al., 2005	[57]	TNF	rs1799724 (TNF), rs1800629 (TNF)	Not in Italy	Alzheimer
Lescai et al., 2010	[58]	PCDH11X	rs5984894 (PCDH11X)	Italy	Alzheimer
Lescai et al., 2011	[59]	**ApoE**	**rs449647 (ApoE), rs769446 (ApoE), rs405509 (ApoE), rs429358 (ApoE), rs7412 (ApoE)**	**Italy**	Alzheimer
Licastro et al., 2011	[60]	IL10, TNF, IL6, IFNG [SERPINA3, HMGCR	–1082G/A(IL10), –308 G/A(TNF), −174 G/C (IL6), +874 T/A (IFNG), –51 G/T (SERPINA 3), –911 C/A(HMGCR)	Italy	Alzheimer
Licastro et al., 2015	[61]	IL-28 b, Med23	rs12979860 (IL-28 B), rs3756784 (MED 23)	Italy	Alzheimer

Table 1. *Cont.*

Name, Year	Ref	Gene	Mutations	Localization	Other
Lio et al., 2003	[62]	IL-10	−1082 G/A (IL-10), −819 C/T (IL-10), −592 C/A (IL-10)	Italy	Alzheimer
Lio et al., 2006	[63]	TNF-α	−308 G/A (TNF-α)	Italy	Alzheimer
Lu et al., 2017	[64]	HLA-DRB1	rs9271192 (HLA-DRB1)	Not in Italy	Alzheimer
Lupton et al., 2016	[65]	TREM2	rs9394721 (TREM2)	Not in Italy	Alzheimer
Maletta et al., 2018	[66]	MTHFR, ACE, AGT, CYP7A1, PAI-1, FII G20210A, FV HR2 H1299R, FV Leiden, GPIIIa, CETP	rs1801133 (MTHFR), rs1801131 (MTHFR), rs1799752 (ACE), rs699 (AGT), 844ins68 (CBS),rs3808607 (CYP7A1), rs1799889 (PAI-1), rs1799963 (FII G20210A), rs1800595 (FV HR2 H1299R), rs6025 (FV Leiden), rs5918 (GPIIIa), rs5882 (CETP)	Italy	Alzheimer
Mariani et al., 2013	[67]	HFE, TF, C282Y	rs1800562 (C282Y), rs1799945 (HFE), rs1049296 (TF)	Italy	Alzheimer
Masri et al., 2020	[68]	PICALM	rs3851179G > A (PICALM)	Not in Italy	Alzheimer
Minoretti et al., 2006	[69]	TLR4	Asp299Gly (TLR4)	Italy	Alzheimer
Montesanto et al., 2016	[70]	UCP2, UCP3, UCP4, UCP5	rs2306820 (UCP3), rs655717 (UCP2), rs660339 (UCP2), rs659366 (UCP2), rs635441 (UCP2), rs1685354 (UCP3), rs2734827 (UCP3), rs1800849 (UCP3), rs10498769 (UCP4), rs12192544 (UCP4), rs3757241 (UCP4), rs9472817 (UCP4), rs17314910 (UCP5), rs6637742 (UCP5), rs3007756 (UCP5), rs5930414 (UCP5)	Italy	Alzheimer
Nacmias et al., 2009	[71]	GAB2	rs2373115 (GAB2)	Italy	Alzheimer
Napolioni et al., 2011	[72]	----------	----------	----------	Not Alzheimer
Olgiati et al., 2013	[73]	SORL1	rs668387 (SORL1), rs68902 (SORL1), rs641120 (SORL1)	NR	Alzheimer
Orlacchio et al., 2002	[74]	NCSTN	237 G/A (NCSTN) 747 C/T (NCSTN)	Italy	Alzheimer
Pilotto et al., 2009	[75]	CYP2D6	rs1080985 (CYP2D6)	Italy	Alzheimer
Pola et al., 2004	[76]	MCP-1	−2518 A/G (MCP-1)	Italy	Alzheimer
Poleggi et al., 2008	[77]	PRNP	Met129- Val (PRNP)	Italy	Alzheimer
Poli et al., 2008	[78]	APH-1b	C + 651T > G (APH-1b)	Italy	Alzheimer
Porrello et al., 2006	[79]	Er-α	PvuII (−397 T/C), XbaI (−351 A/G) (Er-α)	Italy	Alzheimer
Scacchi et al., 2009	[80]	P53, P73	rs1042522 (P53), rs2273953 (P73), rs1801173 (P73), rs3765728 (P73), rs1801174 (P73)	Italy	Alzheimer
Scasellati et al., 2004	[81]	IL-10	−1082 G/A (IL-10), −819 T/C (IL-10), −592 C/A (IL-10)	Italy	Alzheimer

Table 1. *Cont.*

Name, Year	Ref	Gene	Mutations	Localization	Other
Schmidt et al., 2011	[82]	----------	----------	----------	Not in Alzheimer
Schott et al., 2016	[83]	CR1, BIN1, INPP5D, SCARB2, SNCA, MEF2C, CD2AP, EPHA1, NME8, ZCWPW, CLU, PTK2B, CELF1, MS4A4E, PICALM, SORL1, FERMT2, SLC4A4, RIN3, ABCA7, APOE, CD33, EXOC3L2, BLOC1S3, MARK4, CASS4	rs3818361 (CR1), rs744373 (BIN1), rs35349669 (INPP5D), rs6825004 (SCARB2), rs7687945 (SNCA), rs190982 (MEF2C), rs10948363 (CD2AP), rs11767557 (EPHA1), rs2718058 (NME8), rs1476679 (ZCWPW), rs11136000 (CLU), rs28834970 (PTK2B), rs10838725 (CELF1), rs10838725 (MS4A4E), rs10838725 (PICALM), rs670139 (SORL1), rs983392 (FERMT2), rs3851179 (SLC4A4), rs11218343 (RIN3), rs17125944 (ABCA7), rs10498633 (APOE), rs3764650 (CD33), rs2075650 (EXOCL3L2), rs3865444 (BLOC1S3),rs597668 (MARK4), rs7274581 (CAS4)	Not only in Italy	Alzheimer
Scola et al., 2003	[84]	IFN-γ	+874T→A (IFN-γ)	Italy	Alzheimer
Seripa et al., 2008	[85]	GRIN2B	rs1019385 (GRIN2B), rs1806201 (GRIN2B), rs890 (GRIN2B)	Italy	Alzheimer
Seripa et al., 2008	[86]	RELN, LIMK2	rs607755 (RELN), rs2229864 (LIMK2)	Italy	Alzheimer
Seripa et al., 2011	[87]	----------	----------	----------	Review
Serpente et al., 2011	[88]	ORL1	rs1050283 (ORL1)	Italy	Alzheimer
Squillario et al., 2020	[89]	TOMM40, GRM7	rs2075650 (TOMM40), rs8106922 (TOMM40), rs9311976 (GRM7), rs266410 (GRM7)	NR	Alzheimer
Talwar et al., 2021	[90]	ApoE, EGFR, ACTB	rs405509 (ApoE), rs7259620 (ApoE), rs769449 (ApoE), rs725617 (ApoE), rs7256173 (ApoE), rs6970262 (EGFR), rs852423 (ACTB)	Not in Italy	Alzheimer
Tedde et al., 2010	[91]	NEDD9	rs760678 (NEDD9)	Italy	Alzheimer
Tindale et al., 2017	[92]	----------	----------	----------	Not Alzheimer
Tisato et al., 2018	[93]	TF, HFE, FPN1, HAMP	HFE C282Y, HFE H63D, FPN1 −8CG, HAMP −582AG, TF P570S	Italy	Alzheimer
Valenza et al., 2010	[94]	**ApoE**	**−491 A/T (ApoE)**	**Italy**	Alzheimer
Venturelli et al., 2005	[95]	eNOS	T-786C (eNOS)	Italy	Alzheimer
Wang et al., 2016	[96]	GAB2, PICALM, SORL1	rs1010159 (SORL1), rs12285364 (SORL1), rs1699102 (SORL1), rs2070045 (SORL1), rs2282649 (SORL1), rs3824968 (SORL1), rs4935774 (SORL1), rs556349 (SORL1), rs641120 (SORL1), rs661057 (SORL1), rs668387 (SORL1), rs689021 (SORL1), rs3851179 (PICALM), rs541458 (PICALM), rs2373115 (GAB2)	Not in Italy	Alzheimer

NR: not reported.

3.2. Topic 2: The Enigma of Alzheimer's: Investigating Genetic Patterns, Genotypes as a Future Biomarker

The top 30 most relevant terms of this topic (i.e., the most frequent terms within papers grouped in this topic, Figure 9) indicate a research "biomarker", focusing on evaluating SNPs' translation research. Indeed, the twenty-two analyzed articles aimed to elucidate the relationship of SNPs expressed pathological clinical data and evaluate SNPs' potential as biomarkers in AD.

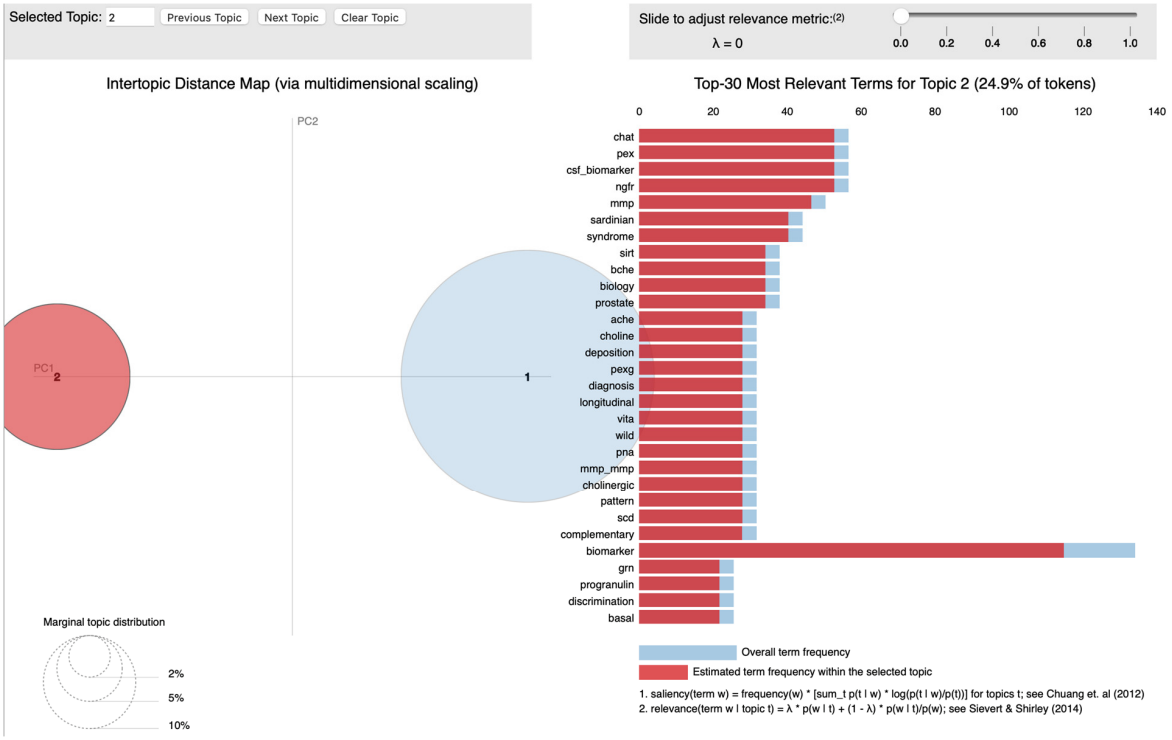

Figure 9. Inter-topic Distance Map related to topic 2. Circle 1 indicates topic 1, circle 2 is topic 2, extracted from the MySLR platform.

For the second topic, we built Table 2, which included the main characteristics of interest to us, intending to evaluate MySLR ability to help us to select papers. Of the twenty-two papers included in topic 2, 13.6% (n = 3) were not carried out in Italy, and we indicated it as "Not in Italy", 4.5% (n = 1) do not specify the origin of the patients and controls, 13.6% (n = 3) are reviews or systematic reviews. The 27.2% (n = 6) were not considered, as they were not conducted in Alzheimer's patients and therefore did not answer the search query. A total of 4.5% (n = 1) of the studies included in topic two concern SNP on ApoE in the Italian population.

Table 2. Overview of the characteristics of the papers included by machine learning in topic two.

Name, Year	Ref	Gene	Mutations	Localization	Other
Bernardi et al., 2012	[97]	----------	----------	----------	Not Alzheimer
Calabretta et al., 2009	[98]	----------	----------	----------	Not Alzheimer
Cheng et al., 2012	[99]	NGFR	rs734194 (NGFR), rs2072445 (NGFR), rs2072446 (NGFR), rs741072 (NGFR), rs741073 (NGFR)	Not in Italy	Alzheimer
De Rojas et al., 2021	[100]	PRKD3/NDUFAF7, SHARPIN, PLCG2, CHRNE, APP	rs876461 (PRKD3/NDUFAF7), rs34674752 (SHARPIN), rs34173062 (SHARPIN), rs3935877 (PLCG2), rs72835061 (CHRNE), rs2154481 (APP)	NR	Alzheimer

Table 2. *Cont.*

Name, Year	Ref	Gene	Mutations	Localization	Other
Flex et al., 2006	[101]	MMP-1, MMP-3, MMP-9	2G2G (MMP-1), 1G2G (MMP-1), 5A5A (MMP-3), TT (MMP-9)	Italy	Alzheimer
Grunbatt et al., 2011	[102]	CHAT	rs10776585 (CHAT), rs2289305 (CHAT), rs3750752 (CHAT), rs12356649 (CHAT), rs11591558 (CHAT), rs8178984 (CHAT), rs1153783 (CHAT), rs1880676 (CHAT), rs12359885 (CHAT), rs8178990 (CHAT), rs10082479 (CHAT), rs17775758 (CHAT), rs7903612 (CHAT), rs7091005 (CHAT), rs2889759 (CHAT), rs4838391 (CHAT), rs11101186 (CHAT), rs10857520 (CHAT)	Italy	Alzheimer
Hansmannel et al., 2010	[103]	OTC	rs5963409 (OTC), rs5963411 (OTC)	Italy	Alzheimer
Hong et al., 2020	[104]	ApoE, LINC01570, TOMM40, LOC124903153, NECTIN 2, LOC107985236, LINC01030, LINC00624, APOC1, ADAMTS3, ADGRB3, FZD4-DT, LOC107984589, SLC2A3, NMNAT2	rs429358 (ApoE), rs10400961 (LINC01570), rs34095326 (TOMM40), rs1004954 (LOC124903153), rs34794167 (LOC124903153), rs6857 (NECTIN2), rs12857276 (LOC124903153), rs7254133 (GRCh38?), rs2209929 (LOC124903153), rs3814341 (LOC107985236), rs2023625 (LINC01030), rs35386129 (LOC124903153), rs2321744 (LOC124903153), rs985017 (LOC124903153), rs769449 (ApoE), rs985018 (LOC124903153), rs36015381 (LOC124903153), rs34528363 (LOC124903153), rs12972970 (NECTIN2), rs12972156 (NECTIN2), rs68058618 (GRCh38?), rs12429500 (LOC124903153), rs6672481 (LINC00624), rs2353964 (LINC00624), rs10900366 (LINC00624), rs12721051 (APOC1), rs12408395 (LINC00624), rs9592217 (LOC124903153), rs9598510 (LOC124903153), rs10900364 (LINC00624), rs11240038 (LINC00624),rs9598511 (LOC124903153), rs6657402 (LINC00624), rs2353972 (LINC00624), rs36055662 (ADAMTS3), rs117950083 (ADGRB3) rs35709873 (LOC124903153), rs56131196 (APOC1), rs4420638 (APOC1), rs55696402 (LOC124903153), rs11605035 (FZD4-DT), rs11606999 (FZD4-DT), rs11607037 (FZD4-DT),rs10898566 (FZD4-DT), rs10898565 (FZD4-DT),rs12999830 (GRCh38), rs11240037 (GRCh38), rs11240043 (LINC00624), rs2075650 (TOMM40), rs34404554 (TOMM40), rs4600098 (LINC00624), rs6684440 (LINC00624), rs4381253 (LINC00624), rs6683579 (LINC00624), rs6657222 (LINC00624), rs2883315 (LINC00624), rs4339909 (LINC00624), rs6696385 (LINC00624), rs11581799 (LINC00624), rs11556505 (TOMM40), rs4375326 (LINC00624), rs11576468 (LINC00624), rs11589438 (LINC00624), rs12742771 (LINC00624), rs11240050 (LINC00624), rs78581038 (LOC107984589), rs12812878 (SLC2A3), rs6695692 (LINC00624), rs6688033 (LINC00624), rs11234901 (FZD4-DT), rs6688244 (LINC00624), rs6678706 (LINC00624), rs11605694 (FZD4-DT),rs58619449 (FZD4-DT), rs58370115 (FZD4-DT), rs7127641 (FZD4-DT), rs61809265 (NMNAT2), rs35519936 (LOC124903153), rs34342646 (NECTIN2),rs10414043 (APOC1), rs72639166 (FZD4-DT),rs7256200 (APOC1)	Not in Italy	Alzheimer
Krumbiegel et al., 2010	[105]	----------	----------	----------	Not Alzheimer
Lambert et al., 2011	[106]	BIN1, EXO3CL2, PICALM	rs744373 (BIN1), rs597668 (EXO3CL2), rs541458 (PICALM)	Italy	Alzheimer

Table 2. *Cont.*

Name, Year	Ref	Gene	Mutations	Localization	Other
Lambert et al., 2013	[107]	FRMD4A	rs7081208 (FRMD4A), rs2446581 (FRMD4A), rs17314229 (FRMD4A)	Italy	Alzheimer
Mazzeo et al., 2019	[108]	----------	----------	----------	Not Alzheimer
Pamio et al., 2020	[109]	CYP2D6	rs1080985 (CYP2D6)	Italy	Alzheimer
Piccardi et al., 2007	[110]	CHAT, AChE	rs2177369 (CHAT), rs12705094 (AChE), rs3087504 (AChE), rs3757869 (AChE)	Italy	Alzheimer
Poli et al., 2005	[111]	ApoE	rs11542041 (ApoE), rs11542035 (ApoE), rs769455 (ApoE)	Italy	Not Alzheimer
Polito et al., 2013	[112]	SIRT2, SIRT3	rs10410544 (SIRT2), rs4980329(SIRT3), rs536715 (SIRT3), rs2015 (SIRT2), rs3825075 (SIRT3), rs11880757 (SIRT2), rs11879010 (SIRT2), rs11667030 (SIRT2)	Italy	Alzheimer
Pozzi et al., 2022	[113]	----------	----------	----------	SR
Rademakers et al., 2007	[114]	GRN, MAPT	Arg493X (GRN), rs1052553 (MAPT), rs7412 (ApoE), rs429358 (ApoE), rs4792937(GRN), rs2879096 (GRN), c.–7–320G→C (GRN), rs34424835 (GRN), rs9897528 (GRN), rs25646 (GRN), c.835 + 7A→G (GRN), rs5848 (GRN), rs34424835 (GRN)	Not in Italy	Alzheimer
Ramos De Matos et al., 2018	[115]	**APOE,** LOC100129500, PVRL2, SNAR-I, TOMM40, INPP5, CD2AP, GLIS3, PVRL2, CASS4	rs35349669(INPP5), rs1316356 (SNAR-1), rs9877502 (SNAR-1), rs9349407 (CD2AP), rs514716 (GLIS3), rs12972156 (PVRL2), rs34342646 (PVRL2), rs71352238 (TOMM40),rs157580 (TOMM40), rs2075650 (TOMM40), rs34404554 (TOMM40), rs11556505 (TOMM40), **rs769449 (APOE)**, **rs429358 (APOE)**, rs439401 (LOC100129500), rs7274581 (CASS4)	Italy *	Alzheimer
Serretti et al., 2007	[116]	----------	----------	----------	Review
Weiner et al., 2015	[117]	----------	----------	----------	Review
Yu et al., 2012	[118]	----------	----------	----------	Not Alzheimer

SR: Systematic Review. * European Studies involving Italy.

Therefore, MySLR, after duplicate removal, allowed us to identify 92 papers divided into two relevant topics characterizing the investigated research area. Despite the current limitations, the available evidence suggests that articles containing studies on AD patients were the 65.22% (n = 60) but the presence of papers about mutations, including SNPs on ApoE gene, for the Italian population was only 5.4% (n = 5)—four of them present in topic 1 and one in topic 2. Therefore, the machine learning used here pointed out five papers work that met our criteria and that we listed in Table 3 specifically.

This approach, which features human-like intelligence, helped us to examine the scientific literature as effectively and rapidly as possible. The machine learning approach allowed us to obtain numerous graphical representations of the data to orient us in choosing the scientific purpose we want. The t-distributed Stochastic Neighbor Embedding (t-SNE) algorithm is shown in Figure 10.

The graph's points symbolize documents (scientific sources), reflecting their similarity concerning a specific topic, each topic is clustered and corresponds to a color (blue and red).

Table 3. Main characteristics of the studies fit our query.

Name, Year	Ref.	Gene	Mutations	Localization
Bizzarro et al., 2009	[33]	ApoE	rs449647, rs405509, rs769446	Italy
Capurso et al., 2010	[38]	ApoE	rs7412, rs429358	Italy
Lescai et al., 2011	[59]	ApoE	rs449647, rs769446, rs405509, rs429358, rs7412	Italy
Valenza et al., 2010	[94]	ApoE	−491 AT vs −491 AA	Italy
Ramos de matos et al., 2018	[115]	ApoE	rs769449, rs429358	Italy *

* European Studies involving Italy.

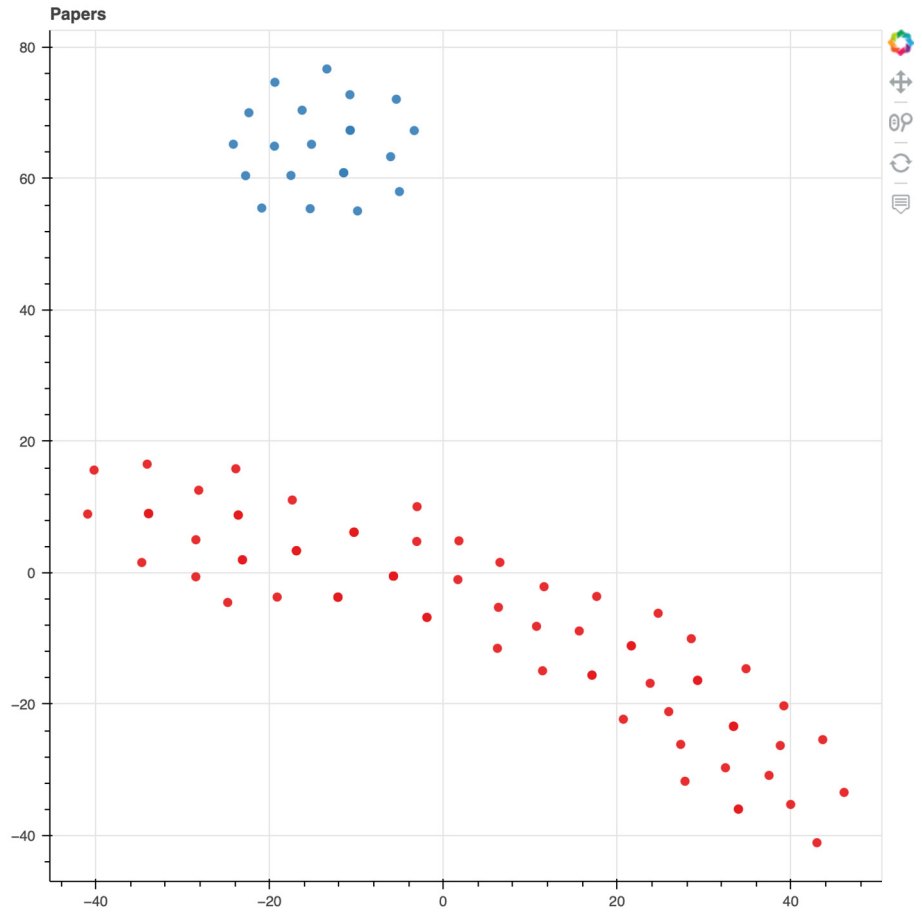

Figure 10. The t-SNE visualization of each topic. The red dots represent the topic one, the blue dots represent the topic two. Produced by MySLR.

4. Discussion

Alzheimer's disease (AD) is a form of dementia and is considered the most frequent type [25]. Genome-wide association studies (GWAS) identified genetic AD mutations [26].

The main objective of this assessment was to evaluate the usefulness of using MySLR machine learning in identifying papers that evaluated the presence of mutations on the ApoE gene in Italian Alzheimer's patients. We did not consider the assessment of mutation

on ApoE systematic reviews and reviews; the latter are indicated in Table 1 as "review" or "systematic review." Several studies were not considered, as they were not conducted in Alzheimer's patients and therefore did not answer the search query; 10% (n = 7) of the studies included in topic 1 concern SNPs on ApoE in the Italian Alzheimer's population. A total of 4.28% (n = 3) did not report the provenience of cases and controls. Many studies, as seen in Table 1, do not specify the SNPs through their nomenclature but indicate the position of the mutation and the consequent amino acid substitution. This phenomenon is probably attributable to the percentage of single nucleotide variation instead of polymorphism, which usually is present in less than 1% of the population harboring variation. The studies that perfectly fit our query have been highlighted in bold in Table 1, along with their reference literature [27–96]. Topic 1 has seventy articles. Several of them contain information on the query made; only six works are not linked to AD [35,44,49,72,82,92]. The majority (four) focus on longevity and APoE [35,49,72,82,92]. In the first, a genome-wide association study (GWAS) was performed for longevity in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium that confirmed APoE and FOXO3 candidacy in this direction [35]. In the second, the genome-wide scan assessment identifies loci for exceptional human longevity [49]. The third paper provides evidence that APoE haplotypes are associated with human longevity in the Central Italy population [72]. The last is to explore genes in lipid and Alzheimer's disease associated with healthy aging and longevity in healthy older populations [92]. In the other two papers, one describes age-related white matter changes [82], and one analyses the cognitive performance and polymorphisms of several genes, including ApoE, in patients with mild cognitive impairment and cognitively healthy controls [44].

Several studies, shown in Table 2, do not specify the SNPs through their nomenclature but indicate the position of the mutation and the consequent amino acid substitution. Studies that perfectly fit our query, even in this case, have been highlighted in bold, which also applies to references [97–117]. Even in this topic, machine learning identified six papers in which AD is not the focus [97,98,105,108,111,118]. In particular, one is related to the epidemiology and genetics factor of frontotemporal dementia assessed by a survey in southern Italy [97], and one is a 7-year follow-up study in subjective cognitive decline and mild cognitive impairment focusing on diverse genes than ApoE [108]. Two works relate to laboratory techniques to assess APoE and study lipid metabolism [98,111]. One correlates ApoE with glaucoma [105] and one is unrelated [118].

The machine learning approach used here helped remove duplicate papers, identify the topic(s), and focus on selecting the papers that interest us. Of the ninety-two papers, only five met our criteria listed in Table 3 [33,38,59,94,115].

In particular, the study of Bizzarro et al. confirmed the role of ApoEε4, harboring the mutation as a Single Nucleotide Polymorphism (SNP) rs449647 A/A genotype, as a risk factor for AD in Italy [33]. In the paper of Capurso et al., the APOE SNPs reported were rs4925 and rs1804834, although they correlate it with other mutations in the glutathione S-transferase omega-1 gene [38].

Lescai and coworkers addressed the relationship between ApoEϵ4, and five SNPs, the rs449647, rs769446, rs405509 in the promoter of the APOE gene, and in ε4 rs429358 and rs7412. Confirming the association between the SNP rs405509 and the AD [59]. Valenza et al., pointed out that APoEϵ4 allele represents the only established genetic risk factor for AD; identified that patients hiding the −491 AA genotype had poorer cognitive performances than the −491 AT ones in the tests of visual attention in AD. This indicates that this mutation has a biological effect more exerted on APOE transcription, and the −491 A/T polymorphism could be considered a disease modifier more than a risk factor for sporadic AD [94]. The last paper is a multicenter study conducted in Denmark, Finland, Germany, Greece, Portugal, Spain, the Netherlands, and Italy. It is the only one of this type, in which ApoEϵ4 allele harbors the SNP rs769449 and rs429358. Therefore, MySLR, with its LDA algorithms, made it possible for us to identify what we were looking for. It is worth noting here that machine learning is widely used in the medical field [119,120]

to identify systematic reviews and meta-analyses or to evaluate the state of the art of a given topic, as it is a helpful tool for simplifying the steps necessary for re-elaboration of complex data contained in the papers. The MySLR platform has already been used to give convincing results previously [121,122]. There are strengths and limitations in our assessment. On the MySRL platform, only key decisions are made transparently and held by humans [21]. The LDA algorithm has been applied in various fields such as medicine, biology, and computer science to extract topics and identify patterns within the literature [121,122]. The use of MySRL offers several strengths, including its ability to reduce the workload involved in the screening phase of a systematic review, making the process more efficient and manageable to analyze large datasets, enabling researchers to identify emerging trends and conduct in-depth topic modeling, and in addition, it allows for the identification of key topics within the literature, which is essential for conducting comprehensive systematic reviews [123–125]. MySLR provides a boost for realizing systematic literature reviews among scientific community members using the LDA algorithm. However, by discarding word order, the LDA algorithm loses specific local context information on semantic relations between words, which might otherwise help interpret deeper meanings and solve ambiguities [126]. A limitation is that LDA assumes that the topics are independent of each other. This is particularly true with topic 2, in our case, in which one paper is unrelated [118] to the context of our research [127,128]. Thus, the analysis did not include correlations between topics or hierarchical structures regarding sub-topics. When applying LDA, it is important to note that the model results are not deterministic. Instead, the results are affected by the researcher's choices regarding the input parameters and built-in stochastic processes. Lastly, an interesting representation coming from MySLR is the t-distributed Stochastic Neighbor Embedding (t-SNE) algorithm. The graph's points symbolize documents (scientific sources), reflecting their similarity concerning a specific topic. These points are grouped into clusters (each topic corresponds to a color—blue and red), highlighting the cohesive thematic relationships among the documents [119]. The t-SNE algorithm is an unsupervised dimensionality reduction technique. This means that the algorithm tries to represent high-dimensional data in a lower-dimensional space, preserving the similarity relations between the original examples without assuming that these relations are linearly distributed.

5. Conclusions

We believe that introducing machine learning, MySLR, will facilitate epidemiologists, physicians, and health professionals' more precise assessment through systematic review and meta-analysis, even following Cochrane's dictates. The semi-automated machine learning platform was able to identify studies related to the query performed on the database with a low percentage of bias. MySLR performed excellently in eliminating duplications and good performance in recognizing keywords linked, in our case, to ApoE mutations in AD.

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