Review article

Hematology Reference Values for *Dicentrarchus labrax* and *Sparus aurata*: A Systematic Review and Meta-Analysis

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ABSTRACT: Hematological parameters are frequently used as physiological indicators in aquaculture studies. These parameters also have extended applications in clinical evaluation, diagnosis, and prognosis in fish health status. However, no normal reference range of values has been demonstrated in depth for any of these hematological parameters for the European sea bass (Dicentrarchus labrax) or gilthead seabream (Sparus aurata). The main objective of this article is to present for the first time through extended literature review, the hematological parameters normal range values for the two most important aquaculture fish species farmed in Mediterranean Sea, D. labrax and S. aurata, and to demonstrate their similarities and their differences. In this article we also discuss the environmental and external factors affecting their normal blood parameters values and we propose fundamental guidelines on the reporting units.

KEYWORDS: *Aquaculture, hemoglobin, hematocrit, guidelines, blood, hematological parameters*

INTRODUCTION

Aquaculture is taking a leading role in addressing global future food availability and security for a growing worldwide population and the associated sustainability challenges. The demand for aquaculture-produced marine fish and high-quality protein is rising due to the stagnation of marine fish catches. According to the FAO (2020), aquaculture is projected to rise to the production of capture fisheries in the future as it reached 46.0 percent in 2016–18 of global fish production, up from 25.7 percent in 2000. Sustainable management that respects the circular economy and climate-driven changes in ecosystems is urgently needed for the aquaculture industry to grow and provide high-quality food. In Mediterranean countries, European sea bass (*Dicentrarchus labrax* L. 1758) and gilthead sea bream (*Sparus aurata*, L. 1758) are of essential economic importance and account for 46.20% of the worldwide production of these 2 farmed fish species (FAO, 2016). These euryhaline and eurythermal species are the key Mediterranean fish produced intensively by aquaculture businesses. Fish farmers aim to boost fish welfare, alleviate substantial economic losses caused by disease outbreaks in aquaculture and provide fish fillets of high nutritional value. The best possible fish farming practices and health controls are essential for successful aquaculture production. Fish health indicators are important to monitor and prevent disease outbreaks. Haematological parameters (i.e., red, white blood cells, thrombocyte counts, haemoglobin concentration and haematocrit) that are influenced by many factors, such as fish ecophysiology and behaviour, can be combined with other environmental factors and provide valuable information and early diagnostic methods to identify stress and prevent or timely diagnose fish diseases and thus improve. fish welfare and decrease economic losses.

Haematogenesis, also known as haematopoiesis, is the process by which blood cells multiply, differentiate, and mature in the haematopoietic organs and are replaced several times throughout one's life. The adequacy of haematopoiesis relies on the physiological ability of haematopoietic stem cells (HSCs) to mature and differentiate (Kondera, 2019). There are several haematopoietic organs in most vertebrates. In avian and mammals, haematogenesis arises primarily in the bone medulla. In reptiles, the bone marrow, liver, and spleen perform this action. Concerning amphibians, blood-forming components in Caudata species take place in the liver, spleen and kidney, while they also take place in the bone marrow in Anura species (Claver & Quagalia, 2009). In all vertebrates, haematogenetic organs also involve the thymus (the site of T-cell maturation). In most Teleostei species, the predominant haematogenetic and storage organ of blood cells is the head kidney (pronephros) (Fijan, 2002; Moritomo et al., 2004). Pronephros are organs analogous to the bone marrow of higher vertebrates; they operate as the principal haematogenetic tissue and lymphoid organ in Teleostei (Stosik & Deptuła, 1993) but are also involved in endocrine functions (Wendalaar-Bonga, 1997; Weytset al., 1999). The head kidney, however, is not the sole haematogenetic organ in fish (Wendalaar-Bonga, 1997; Ivanovski et al., 2009). This haematogenetic function is also accomplished by the spleen and thymus as well as by gut-associated lymphoid tissue (GALT), mucosa-associated lymphoid tissue (MALT) (Barreda et al., 2005; Kobayashi et al., 2007; Ivanovski et al., 2009; Santos et al., 2011) and meso-nephros (Rombout et al., 2005) as shown in carp (Fijan, 2002; Korwin-Kossakowski & Ostaszewska, 2003; Lutnicka & Ludwikowska, 2011). In some fish species, various haematogenetic organs work in parallel, while in others, only one of them is active (Mulero et al., 2009; Patel et al., 2009). For example, only the spleen is haematopoietically active in *Salmo trutta*, and only the kidney is active in *Rutilus rutilus*, while both organs are involved in haematopoiesis in *Perca fluviatilis* (Catton, 1951), in *Oreochromis niloticus* and in *Cyprinus carpio* (Stosik & Deptula, 1993; Homechaudhuri & Jah, 2001). The main blood cell types in fish are erythrocytes (red blood cells), leucocytes (lymphocytes, monocytes, neutrophils, eosinophils, and basophils) and thrombocytes (Genten et al., 2019).

As fish are surrounded by and in intimate contact and interaction with their aqueous environment, they are sensitive to physical and chemical fluctuations of intrinsic and extrinsic factors such as

environmental changes but also fish nutrition or pathologies can affect the morphology and numbers of blood cells (Blaxhall, 1972; Berillis et al., 2016; Clauss et al., 2008). These fluctuations may thus be mirrored in their hematology parameters and the various susceptibility of different fish species or individual may explain the large variability inter- and intra-species found in hematological parameters (Ahmed et al., 2020). Alterations of these haematological parameters rely on quite a few factors, such as species (Ranzani-Paiva et al., 2003; Anthony et al., 2010), sex (Luscova, 1998), age and size (Orun & Endeml, 2002; Jamalzadeh and Ghomi, 2009), stress (Cnaaniet al., 2004), temperature (Langston et al., 2002; Magill & Sayer 2004), photoperiod (Leonardi & Klempau, 2003), nutritional state (Svetina et al., 2002; Lim & Klesius, 2003), reproduction, health status (Vazquez & Guerrero, 2007), water characteristics (Fazio et al., 2012), dissolved oxygen changes (Ranzani-Paiva et al., 2000), lotic or lentic ambients (Val et al., 1985), handling procedures and transport (Gboreet al., 2006), inflammation (Martins et al., 2006) stock density (Vazquez & Guerrero, 2007), and bacterial and parasite infections (Azevedo et al., 2006; Jamalzadeh et al., 2009). The assessment of fish haematological parameters represents a good indicator of the welfare, health and/or pathological status of the fish. The use of standard non-lethal, simple, and cost-effective methods to inspect and assess fish health conditions is fundamental for the growth of fish production (Hrubec et al., 2000). Early disease diagnosis with the use of blood analysis is immensely important because it can offer a trustworthy evaluation via such nonlethal methods (Satheeskumar et al., 2012).

Accurate interpretation of these parameters requires appropriate reference values for each species to reduce the consequences of species differences (Fazio, 2019). Measuring blood parameters is inexpensive and simple to perform, allowing anticipation of the disease by monitoring the physiological, nutritional and health status of the fish (Burgos-Aceves et al., 2019). For an error-free interpretation of fish blood health conditions, it is important to consider a sum of variables, such as reproductive cycle, age, sex, feeding behaviour, stress, nutritional condition, and environmental changes (Satheeskumar et al., 2012; Burgos-Aceves et al., 2019). Furthermore, in aquaculture, the sampling technique, transportation, acclimatization, water characteristics, blood sampling, handling, and storage of blood samples also need to be considered (Fazio et al., 2014; Burgos-Aceves et al., 2019). Although Witeska et al., (2022) reviewed the procedures used in various studies of fish hematology (but only from three articles on *D. labrax* and one on *S. aurata*, none of which fulfilled criteria chosen in the present meta-analysis), the present study deepens this approach by reviewing 45 articles in total (twenty-three for *D.labrax* and twenty-two for *S. aurata*), provides statistical evidence of the influence of non-hematological factors and focuses specifically on the normal reference ranges of the hematological parameters of two Mediterranean fish species.Therefore, the acquisition of contemporary knowledge of *D. labrax* and *S. aurata* haematology with the establishment of physiological reference values under standardized conditions (Burgos-Aceves et al., 2019) will provide a valuable guide to assess the health condition of these two fish species (Maheswaran et al., 2008). To the best of our knowledge, this is the only study that reviews and establishes environmental/physiological ranges of fish haematological parameters. The most recent study provided for cultured and wild fish haematological analysis using an automatic instrument programmed to perform certain functions between various fish species is described by Fazio, 2019. The reference interval for cultured and wild gilthead sea bream *S. aurata* and sea bass *D. labrax* was applied using a restricted number of individuals (up to 50) (Fazio, 2019). The normal reference range of haematologic parameters of these species is presented in several articles either as a part of the research or in reference to a control group. Nonetheless, the presented values vary significantly between research articles questioning what can be considered as a “normal value” (Fazio et al., 2012a; 2012b; 2013; Witeska et al., 2016). The present review also took into consideration the environmental and sampling conditions that could affect these parameters and which could explain some of the discrepancies. Fishes reside in very close encounter with their environment and are therefore sensitive to physical and chemical alterations which may be mirrored in their hematology parameters. Some species are more susceptible to environmental alterations while other have

competent endurance ability which helps them to adopt a strong concept of sustainability (Ahmed et al., 2020).

Proper interpretation of these haematological parameters requires appropriate physiological reference values for both *D. Labrax* and *S. aurata*; therefore, the study of haematological characteristics will be a vital tool for fish welfare and health management in aquaculture. Furthermore, a central goal of this study is to propose guidelines on the reporting units of haematology results and to suggest reference values as a standardization tool to minimize confusion in the presented data. The aim of this review is to study, compare and evaluate the wide ranges of normal haematological parameters in the literature for the two most preponderant aquaculture species farmed in the Mediterranean Sea, the European sea bass (*D. labrax*) and the gilthead sea bream (*S. aurata*).

MATERIAL AND METHODS

Data collection or Bibliographic Search

Haematologic parameters in fish include red blood cell (RBC) count, white blood cell (WBC) count, thrombocyte count (TC), haemoglobin concentration (Hb), haematocrit (Hct) and a group of secondary, calculated indices known as the mean corpuscular values (Grant, 2015). Thus, the mean corpuscular volume (MCV) is the expression of the average volume of individual erythrocytes calculated using the following formula: MCV= (Hct x 10)/RBCs, the mean corpuscular haemoglobin (MCH) is the expression of the average haemoglobin content of a single erythrocyte calculated as: MCH= (Hb x 10)/RBCs and the mean corpuscular haemoglobin concentration (MCHC) is the expression of the concentration of haemoglobin in a given volume of packed red blood cells and is calculated as follows: MCHC= (Hb x 100)/Hct (Docan et al., 2018). The complete blood count profile (CBC) is an indispensable diagnostic instrument, with scientific protocols and reference ranges well documented in both veterinary and human medicine.

A bibliographic search for the current review was conducted through PubMed, Scopus, Google Scholar and Research Gate for articles on haematological analysis in cultured or wild *D. labrax* and *S. aurata*. The following keyword combination was used: (haematology OR haematology OR haematological OR haematological OR blood profile OR blood analysis OR blood cells OR haematocrit OR haematocrit OR haematocrit OR haemoglobin OR red blood cell count OR white blood cells count) AND (European sea bass OR *Dicentrarchus labrax* OR Gilthead seabream OR *Sparus aurata*).Articles on haematological parameters from different websites were also “hand searched” to provide data, and those from internet databases were collected using Google and Research Gate as search engines. A literature search was performed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al.,2009) (Fig. 1). A total of 1670 records were obtained, and 700 records remained after duplicates were removed. Together with 20 more records issued from the personal bibliography, 720 records focusing on studies related to cultured and wild sea bass and seabream were screened. The eligibility of each record was assessed using the following exclusion and inclusion criteria: Articles to be included in the literature review had to present blood analysis data for at least one out of the eight haematological parameters mentioned above on a group of *D. labrax* and/or *S. aurata*. Exclusion criteria were: a. mentioned species other than *D.labrax* and *S. aurata*, b. articles not including haematology parameters, c. using figures instead of values unless mentioned inside the text of the article, d. not presenting statistical data to be used, e. reporting units outside conventional or SI system and transformation to conventional units revealed abnormal values, f. error in calculation of MCV, MCH or MCHC, g. wrong use of haemoglobin kit giving abnormally low values. After screening and eligibility assessment, the total number of studies (n) included in the present meta-analysis was twenty-three (n=23) for *D.labrax*, with weights ranging from 3.71 to 1006 g, and

twenty-two (n=22) for *S. aurata*, with weights ranging from 32 to 359 g, as presented in Table 1 and Table 2, respectively.

Using data from all records included in the present study, we statistically examined the correlation between the blood parameters and fish body weight and found that there was a lack of consistent significant correlations. Specifically, Hb was linked to fish size in sea bass but not in sea bream, while the opposite was true for Hct (i.e., for *D. labrax* RBC/Body Weight Pearson's r: -0.212, p value: 0.298, Hct/BW Pearson's r: -0.036, p value: 0.843, Hb/Body Weight Pearson's r: -0.595, p value: 0.003 and for *S. aurata* RBC/Body Weight Pearson's r: -0.167, p value: 0.522, Hct/Body Weight Pearson's r: 0.426, p value: 0.038, Hb/Body Weight Pearson's r: 0.070, p value: 0.797). Therefore, all haematological parameters were analysed as one-size group.

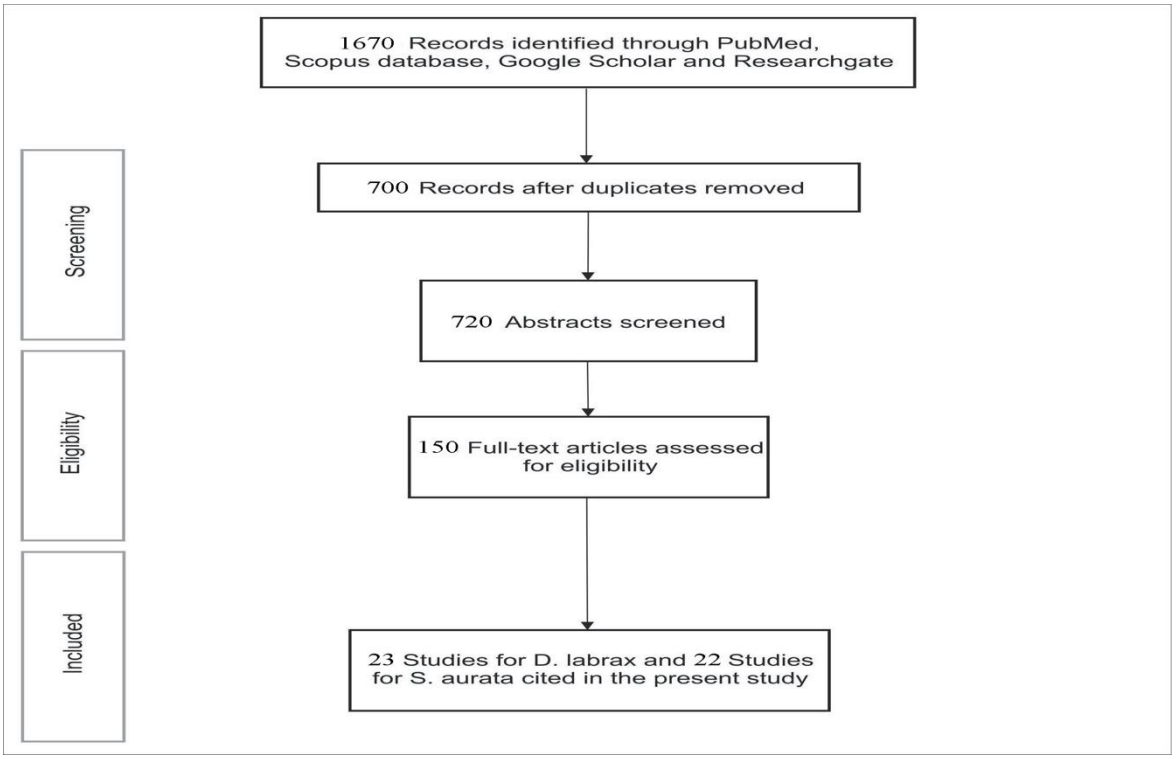

Figure1: Flowchart of included studies illustrates the number of citations and resource materials that have been screened, excluded, or included in this review (PRISMA).

D. labrax and *S. aurata* normal hematology parameters references

D. labrax systematic review of hematology parameters

From the extended research on scientific articles on the "normal" reference ranges of haematological parameters of *D. labrax*, only twenty-three articles met the inclusion criteria mentioned above (Saleh et al., 2015; Goda et al., 2020; Abdelmalek et al., 2015; Saleh et al., 2020; Yilmaz & Ergun, 2012; Marino et al., 2016; Saleh N. E., 2020; Pavlidis et al., 2007; Roque et al., 2010; Roche & Boge, 1996; Yildiz & Altunay, 2011; Filiciotto et al., 2012; Fazio et al., 2018; Fazio et al., 2013; Vectesi et al., 2012; Cotou et al., 2012; Garcia et al., 1992; Buscaino et al., 2010; Petochi et al., 2011; Machado et al., 2019; Caruso et al., 2011; Peruzzi et al., 2005; Alvarez-Pellitero & Pinto, 1987). Not all articles covered all the haematological parameters researched. The calculated parameters MCV, MCH, MCHC and TC had numerically few values; MCV, MCH and MCHC were measured

in eleven out of twenty-three articles, and thrombocyte counts were measured in only six. The remaining haematological parameters RBC, Hb, Hct, and WBC were studied in detail in most articles (Table 1).

S. aurata systematic review of hematology parameters

From the extended research on scientific articles on the "normal" reference ranges of haematological parameters of seabream, only twenty-two articles met the inclusion criteria (Guerreiro et al., 2016; Marino et al., 2016; Goncalves et al., 2020; Henry et al., 2015; Montero et al., 2001; Ballester-Lozano et al., 2015; Gellibolou et al., 2018; Tort et al., 2002; Perez-Sanchez et al., 2015; Rigos et al., 2013; Fazio et al., 2018; Molinero & Gonzalez, 1995; Palstra et al.,2020; Buscaino et al., 2010; Fazio et al., 2015; Yildiz & Alunay, 2011; Pages et al.,1995; Mente et al., 2012; Zupan et al., 2015; Pavlidis et al., 2007; Fazio et al., 2013; Gultepe et al., 2012). Again, only a few articles covered all the haematological parameters considered. The parameters MCHC and TC have been investigated the least in the twenty-two articles included in this review. MCHC was measured in ten out of twenty-two articles, and thrombocytes were measured in only five. The rest of the haematological parameters were investigated in detail in most articles (Table 2).

Statistical Analysis

Correlation analysis was performed on all selected studies to assess whether fish body weight was associated with selected haematological parameters. Due to a lack of consistent significant correlations, we proceeded without adjusting for body weight. Mean values and corresponding 95% confidence intervals (Cis) were calculated for each parameter of the individual studies included in the present meta-analysis. The random effects model was employed (Riley et al., 2011). Forest plots were generated to provide a visual representation of the different normal reference values and the synthesized overall values. All analyses were carried out using JASP Software, version 0.16.1 (University of Amsterdam, Netherlands).

Heterogeneity and publication bias

The I-squared (I^2) test was used to determine variation across the included studies due to heterogeneity rather than chance. I^2 values of <25% are considered low risk, 50% moderate risk, and >75% show a high risk of heterogeneity (Higgins et al.,2003). Publication bias was evaluated by visual inspection of the funnel plot for all outcomes with Egger's regression test (Egger et al., 1997).

RESULTS AND DISCUSSION

Fish hematological analysis is an inexpensive and very useful tool for evaluating fish health and physiological status (Witeska et al., 2022). The present systematic review and meta-analysis reports and compares for the first-time normal haematology parameter reference range values in two major Mediterranean aquaculture species, *D. labrax* and *S. aurata.*

From the meta-analysis of *D. labrax*'s blood parameters presented in the forest plots shown in Figures 2&3, it is obvious that all selected parameters showed highly significant heterogeneity, with I^2 values above 99%. This means that the reviewed articles had a high risk of heterogenicity and publication bias at an extreme percentage, underlining the importance of defining general guidelines for control design and experimental setup. Nevertheless, many conclusions can be drawn from the meta-analysis of these blood parameters based on the mean and the 95% confidence intervals (CI) for each parameter as presented for each parameter's forest plot. Mean and confidence intervals were 3.23 x 10^6/μL (2.81-3.65) for RBC, 30.07 x 10^3/μL (20.83-39.30) for WBC, 8.87 g/dL (7.83-

9.90) for Hb, 35.87% (32.30-39.44) for Hct, 115.05 μm^3 (104.07-126.04) for MCV, 27.48 pg (24.86-30.10) for MCH, 24.57 g/dL (20.69-28.46) for MCHC, and 52.81 x $10^3/\mu L$ (32.21-73.41) for TC (Figure 2&3). These values can be considered the "normal" or "physiological" values of relevant haematological parameters for European sea bass.

From the classical meta-analysis of *S. aurata'*s blood parameters presented in the forest plots shown in Figures 4&5, the heterogenicity of all haematological parameters was evident, as observed for *D. labrax.* Indeed, the articles in the present review all presented a high risk of heterogenicity and publication bias, with I^2 values above 99%. However, solid assumptions can be retrieved from the meta-analysis of the blood parameters from the mean and 95% confidence intervals, as seen on each forest plot. The "normal" or "physiological" values for RBC were 2.96 x $10^6/\mu L$ (2.70-3.22), for WBC, 49.05 x $10^3/\mu L$ (32.22-65.98), for Hb, 8.59 g/dL (7.20-9.98), for Hct, 36.91% (31.66-42.17), for MCV, 137.35 μm^3 (120.29-154.41), for MCH. 28.91 pg (24.86-32.96), for MCHC, 21.26 g/dL (18.68-23.83), and for TC, 49.13x $10^3/\mu L$ (24.20-74.06) (Figure 4&5).

The results of the meta-analysis allow for a comparison of the blood parameter values between the two species *D. labrax* and *S. aurata*. As seen from Figures 2-5, the mean values and their 95% confidence intervals are very close and, in some cases, nearly identical. However, we cannot overlook the difference between the two species in the means of WBC and MCV parameters, even though their CI ranges overlap. We strongly emphasize the importance of the mean values and CI intervals for all the parameters presented, and future scientific research on *D. labrax* and *S. aurata* blood indices should have values close to the values presented here. Values far outside the lower or higher range will caution authors about potential health issues of the fish used in their study or problems with the measuring techniques or inaccuracies.

Fish blood haematological parameters can be affected by many different parameters, such as environmental (water temperature, salinity, nitrate, photoperiod, dissolved oxygen, quality and rate of food consumed) or study design parameters (fish species, size, sex, diet, feeding rate, RAS or flow-through onshore, offshore cages, stress), sampling procedure (anaesthesia, anticoagulant, volume of blood extracted) or even haematological measurement techniques (manual or automated), as listed in Tables 2& 4, and obviously by pathological agents, as haematological parameters are good indicators of fish health status. Indeed, water quality, available oxygen and food quality/supply are important factors that affect fish health and welfare. In European sea bass, Ht and Hb were significantly reduced, and WBC-RBC were significantly increased after a viral infection, while granulocyte numbers increased significantly in fish infected by both virus and parasites, and lymphocyte numbers decreased significantly in fish infected by virus, bacteria and parasites but not by virus alone (Alvarez-Pellitero et al., 1987).

Some research studies have investigated in more depth some of these non-pathological parameters, which may explain discrepancies between haematological studies of "control" fish, although the use of different anticoagulants and different temperatures are investigated in the same reference (Tables 2, 4). Hematological parameters are sensitive to environmental changes and provide information about fish physiological disturbances before the development of their external symptoms, thus pre-analytic and analytic factors may affect the results (Witeska, 2022). Therefore, experience and care is essential to obtain consistent and reliable hematological data. Several studies have shown the association of fish size with haematological parameters. For example, Hct was shown to increase (Garcia et al., 1992; Dendrinos & Thorpe, 1985) or decrease (Zanuy & Carrillo, 1985) with fish size. The present meta-analysis, however, based on a large number of data, showed no consistent significant relationship of the fish size with the blood parameters presented here in either of the two species (i.e., for *D. labrax* RBC/body weight Pearson's r: -0.212, p value: 0.298, Hct/BW Pearson's r: -0.036, p value: 0.843, Hb/body weight Pearson's r: -0.595, p value: 0.003 and for *S. aurata* RBC/body weight Pearson's r: -0.167, p value: 0.522, Hct/body weight Pearson's r: 0.426, p value: 0.038, Hb/body weight Pearson's r: 0.070, p value: 0.797). Therefore, the results of all fish sizes were analysed and presented together.

One of the most important factors that has been reported to significantly affect blood parameters is temperature. Seasonal variation probably related to water temperature and photoperiod affects fish hematocrit and leucocrit (Pascoli et al., 2011). These results provide a better understanding of the influence of seasonal variation on the immune system and hematological parameters in fish to optimize fish husbandry management in aquaculture when fish response is seasonally less efficient. Temperature has consistently been identified as the primary abiotic factor controlling key physiological, biochemical, and life-history processes in fish (Beitinger & Fitzpatrick, 1979). It has been mentioned that in rainbow trout during warm periods, haematological parameters such as Hb, Hct and RBC are slightly lower than in the cold season, which can be linked to an elevated O_2-carrying capacity and O_2 demand (Burgos-Aceves et al., 2019). The association of temperature with some haematological parameters has been evaluated in one study in European sea bass and two studies in Gilthead seabream through seasonal studies where many other factors can fluctuate together with temperature (Fazio et al.,2018) or simultaneous studies in parallel systems kept at different temperatures (Guerreiro et al., 2016), the latter being more reliable to assess the association of temperature independently of other factors fluctuating with the season. This study demonstrates that temperature has a marked relationship with haematological parameters, and a 7 °C temperature increase to reach *Sparus aurata* optimum of 25 °C significantly increased red blood cell counts and haematocrit and haemoglobin concentrations but reduced white blood cell counts (Guerreiro et al., 2016).

In the present review concerning *D. labrax*, we can cross-evaluate the relationship of temperature with some haematological parameters. In detail, at low temperatures, as seen in the articles of Fazio et al., 2018 with temperatures of 13.40 ± 0.18^0 C, in Roche & Boge, 1996 with temperatures of 15 ± 1^0 C, Garcia et al., 1992 with temperatures of 16.5 ± 1.0, and in Goda et al., 2020 and Yildiz and Altunay, 2011 with temperatures of 18 ± 1^0 C, the haematological parameters vary significantly, with haemoglobin values ranging from 7.65 ± 0.05 g/dL (Goda et al., 2020) to 10.60 ± 1.10 (Fazio et al., 2018), RBC values ranging from $1.36 \pm 0.02 \times 10^6$/μL (Goda et al., 2020) to $4.01 \pm 0.60 \times 10^6$/μL (Fazio et al., 2018), and haematocrit values ranging from 18.59 ± 0.07% (Goda et al., 2020) to 32.9 ± 0.9% (Roche & Boge, 1996) and 48.38 ± 4.81% (Fazio et al., 2018).

The same observation of a wide range of haematological values was also seen at higher temperatures. In more detail, in the articles of Fazio et al., 2018 with temperatures of 23.20 ± 0.22^0 C, in Saleh et al., 2020 with temperatures of 24.4 ± 1.2^0 C, Machado et al.,2019 with temperatures of 25.4 ± 0.5^0 C and Roque et al., 2010 with temperatures of 26.5-27.5 °C, the haemoglobin values range from 6.67 ± 0.87 g/dL (Fazio et al., 2018) and 7.36 ± 0.60 g/dL (Machado et al., 2019) to 12.77 ± 0.25 g/dL (Saleh N.E., 2020), RBC values range from $2.92 \pm 0.18 \times 10^6$/μL (Machado et al., 2019) and $3.02 \pm 0.66 \times 10^6$/μL (Fazio et al., 2018) to $4.63 \pm 0.07 \times 10^6$/μL (Saleh N.E. 2020), and haematocrit ranges from 28.33 ± 1.69% (Machado et al., 2019) and 32 ± 3.48% (Fazio et al., 2018) to 45 ± 2.58% (Saleh N.E., 2020). From all the above articles, no clear and distinct association of temperature ranging from as low as 13.40^0 C to as high as 25.4^0 C could be observed on *D. labrax* blood parameters, as presented in Table 1.

A wide range of values in haematological parameters, such as haemoglobin, RBC and haematocrit, at different temperatures can also be seen in *S. aurata*. In detail, at low temperatures, as seen in the articles of Tort et al., 2002 with temperatures of 15^0 C ± 0.5, in Pages et al., 1995 with temperatures of 15 ± 0.5^0 C, and in Molinero and Gonzalez, 1995 with temperatures of $15\text{-}16^0$ C, the haematological parameters vary significantly, with haemoglobin values ranging from 4.16 ± 0.6 g/dL (Molinero & Gonzalez, 1995) and 4.55 ± 0.42 g/dL (Tort et al.,2002) to 7.49 ± 0.42 g/dL (Pages et al., 1995), RBC values ranging from $2.23 \pm 0.11 \times 10^6$/μL (Tort et al., 2002) to $2.80 \pm 0.13 \times 10^6$/μL (Pages et al., 1995), and haematocrit values ranging from 21.34 ± 1.42% (Tort et al., 2002) and 25.80 ± 2.5% (Molinero & Gonzalez, 1995) to 32.10 ± 1.1% (Pages et al., 1995).

At higher temperatures, the same wide range of values can be distinguished. In more detail, at high temperatures, as seen in the articles of Fazio et al., 2018 with temperatures of 23.2 ± 0.22^0 C, in

Ballester-Lozano et al., 2015, with temperatures of 24^0 °C, and Gelibolu et al., 2018, with temperatures of 24.77 ± 0.18^0 C, the haemoglobin values ranged from 7.16 ± 0.47 g/dL (Ballester-Lozano et al., 2015) to 9.62 ± 0.74 g/dL (Fazio et al., 2018) and to 11.86 ± 0.15 g/dL (Gelibolu et al., 2018), RBC values ranged from 2.66 ± 0.07 x 10^6/µL (Ballester-Lozano et al., 2015) to 3.01 ± 0.04 x 10^6/µL (Gelibolu et al., 2018) and to 3.48 ± 0.51 x 10^6/µL (Fazio et al., 2018), and haematocrit ranged from 32.80 ± 1.68% (Ballester-Lozano et al., 2015) to 42.52 ± 5.12% (Fazio et al., 2018) and to 61.33 ± 2.01% (Gelibolu et al., 2018). From the above observations, temperatures ranging from 15 °C to 27 °C seem to increase some blood parameters, such as Hb and RBC of *S. aurata*, as presented in Table 3, but no statistical evidence can be obtained from this type of analysis. In the natural fish environment, a water temperature increase is linked to a decrease in dissolved oxygen, and thus, an increase in temperature may require the fish to increase RBC counts and Hb concentrations so as to efficiently capture and transport the low levels of oxygen available.

Another important factor that may influence the haematological parameters of fish is salinity, which is considered a determining growth and survival element in fish aquaculture (Lisboa et al., 2015; Baliarsingh et al., 2018). Salinity stresses can be associated with haematological alterations and can have a physiological impact on the immune system (Choi et al., 2013). In Nile tilapia exposed to a hyperosmotic environment, the haematological parameters Hct, Hb and RBC tended to decrease, probably because of changes in the water content in the blood (Bosisio et al., 2017; Elarabany et al., 2017). The reduction in RBC, Hb, and Hct parameters may be associated with salinity-induced osmoregulatory dysfunction (Girling et al., 2003), and a reduction in WBC could be linked to haemorrhagic injury caused by variation in salinity (Anyanwu et al., 2007). In the present systematic review, the salinity range in articles dealing with *D. labrax* was between 28 and 40 g/L and 30 to 42 g/L concerning *S. aurata.* In *D. labrax* specifically, the lowest salinity was presented by Yilmaz & Ergun, 2012 with 28.2 ± 0.2 g/L and Marino et al., 2016 with 30 g/L. On the highest salinity, with a range from 37.8 to 40 g/L, there were 7 articles with varying values of haematological parameters (Table 1).

In *S. aurata* specifically, the lowest salinity was presented by Marino et al., 2016 (30 g/L) and the highest by Pages et al., 1995 (42 g/L). The haematological values for both articles were 3.77 ± 0.13 x 10^6/µL and 2.80 ± 0.13 x 10^6/µL for RBCs, 11.75 ± 0.29 g/dL and 7.49 ± 0.42 g/dL for Hb, 43.62 ± 1.37% and 32.10 ± 1.1% for Hct, 116.10 ± 2.65 µm^3 and 115.4 ± 4.20 µm^3 for MCV, 31.29 ± 0.48 pg and 26.1 ± 2.5 for MCH and 27.07 ± 0.48 g/dL and 23.4 ± 2.0 g/dL for MCHC, respectively. According to these results, there could be a trend for decreased haematological parameters with increasing water salinity, especially for S. *aurata.* However, the increased salinity of 42 g/L is close to the optimal range of the Mediterranean Sea of 38-40 g/L, and the salinity range covered by the included studies was not particularly wide. Therefore, the differences between the haematological parameters in both species (Tables 1 &3) cannot be explained solely by those salinity ranges.

Another equally important factor that may affect haematological parameters is dissolved oxygen (DO). In *D. labrax,* the DO ranged from 3.8 ± 0.05 mg/L to 9.8 ± 1.1 mg/L and in *S. aurata* from 3.8 ± 0.05 mg/L to 12 mg/L. The lowest DO values in *D. labrax* were presented by Fazio et al., 2018 and by Pavlidis et al., 2007. The haematological values in those articles were 3.02 ± 0.66 x 10^6/µL and 4.01 ± 0.60 x 10^6/µL for RBCs, 6.67 ± 0.87 g/dL and 10.60 ± 1.10 g/dL for Hb, 32 ± 3.48% and 48.38 ± 4.81% for Hct, 109.40 ± 18.43 µm^3 and 122.20 ± 14.66 µm^3 for MCV, 23.28 ± 6.60 pg and 26.62 ± 3.62 pg for MCH, and 21.07 ± 3.41 g/dL and 21.96 ± 1.53 g/dL for MCHC. The highest DO values were presented by Yildiz and Altunay, 2011 at 12 mg/L and from Petochi et al., 2011 at 9.8 ± 1.1 mg/L. Unfortunately, there is a lack of haematological data presented by the authors, except for the Hct with values of 30.78 ± 4.41% and 30.7 ± 1.8%, respectively, and an Hb value of 10.2 g/dL only from Petochi et al., 2011. Values of 7 to 8 g/dL were presented by most of the remaining articles that measured DO (Table 2). In *D. labrax,* low or high DO values could not be clearly linked to changes in blood parameters presented by these authors.

In *S. aurata*, the lowest values of DO were presented in Fazio et al., 2018 with 3.8 ± 0.05 g/dL and Fazio et al., 2015 with 5 g/dL. The haematological values in those articles were 3.48 ± 0.51 x 10^6/μL and 2.74 ± 0.13 x 10^6/μL for RBCs, 9.62 ± 0.74 g/dL and 9.07 ± 0.44 g/dL for Hb, 42.52 ± 5.12% and 49.83 ± 2.51% for Hct, 124.50 ± 20.22 μm^3 and 181.60 ± 1.99 μm^3 for MCV, 28.26 ± 4.77 pg and 33.05 ± 0.74 pg for MCH, and 22.91 ± 3.22 g/dL and 18.34 ± 0.61 g/dL for MCHC. The highest DO values were presented by Gelibolu et al.,2018 with 11 ± 0.16 mg/L and by Yildiz & Altunay, 2011 with 12 mg/L. Gelibolu et al., 2018 reported haematological results of 3.01 ± 0.04 x 10^6/μL for RBCs, 11.86 ± 0.15 g/dL for Hb, 61.33 ± 2.01% for Hct, 204.17 ± 6.76 μm^3 for MCV, 39.63 ± 0.23 pg for MCH and 19.33 ± 0.54 g/dL for MCHC, while Yildiz & Altunay, 2011 provided only a Hct value of 29.23 ± 3.95%. From the values presented from low and high DO, there was no clear relationship of low DO with haematological parameters. The lower values of RBC and Hb at very high DO levels may be explained by the fact that large RBC and Hb concentrations in RBCs are not needed to absorb the largely available oxygen dissolved in the surrounding water. The extremely elevated Hct percentage (61.33 ± 2.01%) at high DO obtained by Gelibolu et al., 2018 was not obtained by Yildiz & Altunay, 2011. In other fish species, i.e., European catfish (*Silurus glanis*), many authors claim that reduced DO caused reduced blood parameter values, while increased DO caused increased RBC, WBC and Hb values but reduced Hct (Docan et al., 2010, Kucukgul et al., 2019). In *S. aurata*, as in *D. labrax*, low or high DO presented in the articles reviewed did not clearly affect the blood parameters.

Sampling procedures such as the use of different anaesthetics can affect the stress status of the fish and may therefore affect the physiological response of the fish. Best practice for fish blood sampling has been reviewed recently by Lawrence and colleagues (2020). Anaesthetics such as MS 222,2-phenoxyethanol, clove oil, AQUI-S, and ice have been used in various studies. Although anaesthetics may have distinctive effects on the haematological parameters, we could not discriminate any clear pattern from the use of one against another compound when comparing those studies. A study in seabream, however, compared the effects of clove oil and phenoxyethanol (2-PE) to a control without anaesthesia (Tort et al., 2002). Clove oil was shown to be a better anaesthetic agent than phenoxyethanol (2-PE) in seabream, as it did not significantly affect Hct, Hb, RBC or MCV, MCH and MCHC at any of the 3 concentrations tested compared to a control without anaesthesia as opposed to 2-PE (Tort et al., 2002), but the choice of the control may not be the most appropriate. The preferred use of clove oil over other anaesthetics was also shown in vimba bream (*Vimba vimba*) (Lepic et al., 2014). Other sampling factors that may affect the haematological results include the volume of blood sampled. This was investigated in sea bass, and Hct was shown not to be affected whether 0.5, 1 or 2 ml blood was collected or if two consecutive blood extractions were subsequently performed. It was interesting to see that this was not the case in rainbow trout, where the volume of blood sampled significantly affected Hct (Garcia et al., 1992). Additionally, the anticoagulants used with the blood of *D. labrax* and *S. aurata* were heparin or EDTA. In particular, 12 of the studies on *D. labrax* used heparin, and 9 used EDTA, while 11 and 6 studies in *S. aurata* used heparin and EDTA, respectively. Heparin binds to the enzyme inhibitor antithrombin III, and this complex assembly accelerates the inactivation of thrombin and Factor X to prevent the formation of fibrin from fibrinogen. Heparin tends to cause white blood cell clumping and a faint blue background in Wright-Giemsa stained smears and is particularly known to interfere with PCRs. EDTA acts by strongly binding calcium in the blood, which inhibits the clotting process while preserving the cellular components and morphology of blood cells. (eClinPath.com, 2013). Heparin is not recommended as an anticoagulant for cell counts, because the cells clump in heparin, invalidating WBC counts and differential cell counts, and in that respect, it is not safe to suggest heparin as the anticoagulant of choice as proposed by Witeska et al., 2022. Also, citrate is not recommended due to the dilution of the blood by the liquid citrate. However, there are certain fish species whose blood may hemolyze on contact with EDTA (Witeska & Wargocka, 2011). For these species, blood can be collected directly from the needle into citrate anticoagulant. However, the correct citrate to blood ratio must be maintained, i.e. 1 part citrate to 9 parts blood. Ideally, the citrate should be placed into the syringe and the appropriate volume of blood withdrawn directly

into anticoagulant (eClinPath.com, 2013). From the above, we can conclude that all the anticoagulants mentioned above have their limitations and further studies in fish are needed in the future or a new anticoagulant able to meet the unique requirements of fish hematology must be developed.

Concerning other stresses, haematocrit and haemoglobin were not significantly affected in European sea bass exposed to short-term (4 days) hypercapnia but decreased after chronic hypercapnia (45 days) (Petochi et al., 2011). Short-term exposure to nitrate was shown to decrease WBC and lymphocyte counts and increase RBC, Hb and thrombocyte numbers in European sea bass (Vectesi et al., 2011). The increased number of RBCs accompanied by a reduction in their size as assessed by MCV may be linked to the release of new small RBCs into the circulation by the head-kidney, thymus and/or spleen (Kori-Siakpere & Ubogu, 2008; Kondera, 2019). The increased thrombocytes may prepare the fish for blood loss through the gills due to exposure to toxicants (Frisch & Anderson 2000). In gilthead seabream, acute handling stress was shown to increase RBC, Hct, Hb and WBC (Fazio et al., 2015). A 7-day-long copper exposure was shown to significantly increase the haemoglobin concentration of European sea bass (Cotou et al., 2012). Acute stress is usually expected to increase Hct and Hb to increase the oxygen supply in response to the higher metabolic demands of the major organs (Cnaani et al., 2004), while chronic stress is usually considered to overwhelm the fish physiological response and may be translated into a decrease in Hct or other haematological parameters. The antibiotic bath treatment also represents a common stressor in aquaculture settings to both *D. labrax* and *S. aurata*, as shown through an elevated cortisol response, which was not accompanied by any change in Hct values for either of the two investigated fish species (Yildiz & Altunay, 2011). Acoustic stimuli were also investigated in both sea bass and seabream and were shown to significantly increase the haematocrit of both fish species (Buscaino et al., 2010). The effect of stress on the haematological parameters of Mediterranean fish species will require further studies to investigate whether acute and chronic stress of different types have consistent effects on the fish haematological status that may be better understood in the future based on the present establishment of physiological ranges for European sea bass and gilthead seabream. It was also interesting to see that factor intrinsic to the fish, such as fish sex or triploidy, may affect the haematological parameters, which would suggest that normal ranges should be determined for different fish sexes or genomic natures. Triploidization of sea bass was shown to significantly increase erythrocyte size but to decrease RBC and Hb concentrations with subsequent increases in MCV and MCH (Peruzzi et al., 2005).

At this point, it is essential to propose and present fundamental guidelines on the reporting units of haematology results and to encourage the use of the same units worldwide to minimize confusion on presented data. In Table 5, we display our recommendation for the reporting units in the blood count, in either conventional or SI unit forms along with the conversion factor to SI unit. Similar efforts were made by the International Council for Standardization Council in Haematology (ICSH) for human laboratory haematology units (Brereton et al., 2016).

From this systematic review and meta-analysis, the need to determine precise reference values of the haematology parameters for both species, *D. labrax* and *S. aurata*, is clear. In addition, all the articles in this systematic review refer to blood parameters measured on clinically healthy specimens (controls) but not in standardized environmental conditions or sampling or measuring techniques, and those discrepancies may account for some of the differences between studies. It was therefore decided to present the environmental parameters and experimental conditions in Tables 2 and 4 for *D. labrax* and *S. aurata*, respectively. Thus, the increased heterogenicity and publication bias, as is clearly evident from the statistical meta-analysis, reveals the lack of comprehensive and thorough research on the normal haematology parameter reference values until now. This is the first time a challenging task such as a systematic review and meta-analysis in haematology of these two important Mediterranean species has been apprehended. The meta-analysis results presented here regarding the mean and 95% CI of all blood parameters present normal values for the most relevant

haematological parameters of both species, as presented in Figures 2-5. The similarities between the two species' normal reference range values for the majority of the haematological parameters can be explained on the basis that both species live in the same Mediterranean environment and habitats, have nearly the same diet in the wild or in aquaculture facilities and have very similar biometric growth indices and parameters.

Hematology in farmed fish: future perspectives and analytical difficulties

Fish haematology parameter interpretation, despite worldwide booming evolution in fish veterinary medicine, is still lacking because of the lack of reference values and lack of standardized collection and measurement techniques (Kori-Siakpere et al., 2005). The total blood volume of fish is smaller than that of other vertebrates. Fish erythrocytes are similar in size and structure to the erythrocytes of other vertebrates, but they are nucleated. Fish thrombocytes are also nucleated. These two fish cell types are therefore not recognised as such by haematological analysers which are calibrated for mammals, reptiles, or birds, thus complicating the interpretation of the results. Moreover, nuclei from lysed fish erythrocytes and thrombocytes are similar in size to lymphocytes which can thus be overestimated with the use of automatic cell counters (Fazio et al., 2019). Furthermore, due to the similar morphology of WBCs and TCs, it is difficult to differentiate them, and some authors assimilate thrombocytes to WBCs (Ueda et al., 1997). The use of these automatic analysers for fish, require special software modifications (Fazio et al., 2012a). Calibration of these automatic analysers may become available for different fish species in the near future and the values collected in the present review may represent a useful reference for this process to take place for *D. labrax* and *S. aurata*. In addition, the vast diversity of fish species makes the problem worse (Clauss et al., 2008). In order to use haemocytometers for fish blood cell measurements, calibration of the apparatus must be adapted to each species (Witeska et al., 2022) and special attention must be given to the sample preparation and measurement calculations. Because of the high density of the cell, dilution of the blood must take place. The dilution that is usually performed is 1:200 blood/isotonic solution (usually 10 μl of blood is used for the dilution). After dilution, viability dyes, such as erythrosine B or trypan blue, must be added. White blood cells are counted in the four corner squares of the haemocytometer, while erythrocytes are counted in the central square, where smaller squares are drawn (Absher, 1973; Khan et al., 2012). A general rule, for both erythrocytes and white blood cells, is that someone can count the cells touching the top and left of the squares and skip the ones at the bottom and right. To calculate the number of cells per μl of blood, a multiplication of the measured cell numbers (erythrocytes or white blood cells) by a factor depending on the dilution applied to the original sample must be performed. Variations due to pipetting, dilution, non-uniform cell distribution and counting errors are very common with the use of a haemocytometer (Biggs & MacMillan, 1948). Also, particular care should be applied to the conversion between SI units and conventional units used in haematology, because it was responsible for many mistakes in the past, particularly concerning the assessment of haemoglobin, MCV, MCH, and MCHC.

It is evident for both farmed species that there was a lack of comprehensive and detailed examination of all blood parameters. Many of the reviewed articles rely on only one or two haematological parameters. As presented in this article, all blood parameters are equally important, and each one, alone and in combination with each other, provides different but essential information regarding the health condition of the fish and is an invaluable diagnostic method as a whole. If authors choose to investigate selective blood parameters, they may be prone to clinical errors, thus narrowing their diagnostic field, and this may create a tremendous danger of misinterpretation of their research and misdiagnosis in the aquaculture industry with potential economic risks and hazards.

Hematological analyses such as Hct and WBC are relatively easy to perform on site as they require small equipment (microcentrifuge, microscope) that can be easily purchased by fish farms. A small variation of these parameters may annunciate some pathological concern and should prompt fish farmers to call on a veterinarian to readily perform a more precise diagnostic and apply quicker a therapy that may prevent fish loss with the economic loss that comes together.

CONCLUSION

In conclusion, this systematic review and meta-analysis of a total of 45 articles with haematological indices of healthy individuals provides solid data on normal reference range values of the most important haematological parameters. We have been able to present the mean and CI ranges for those normal haematological indices for both *D. labrax* and *S. aurata*. Extreme values outside of these ranges will warn researchers that either there is a problem with the health status of the fish or with the analytical technique or the calculations. Additionally, we have been able to propose guidelines on reporting units used in either conventional or in SI systems. The use of either conventional or SI units is strongly recommended and will help the harmonization of research in fish haematology science. Furthermore, we thoroughly investigated the 45 articles of both species reviewed, and the association of some extrinsic parameters with the haematological indices revealed that each important factor, such as size, salinity, DO, anaesthetics, or anti-coagulants, may not account for the deviation from normal values. In contrast, temperature seemed to be significantly associated with *S. aurata* blood parameters, a relationship that was not so clear in the case of *D. labrax*, which may reveal a higher sensitivity of *S. aurata* to temperature variation compared to *D. labrax*.

Nevertheless, more studies are needed to make necessary adjustments to the mean haematological physiological reference values and the confidence intervals of the two major Mediterranean species, *D. labrax* and *S. aurata*, produced by the Mediterranean aquaculture industry, and this should be facilitated if the present guidelines are followed in future haematological studies.

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Table 1. Hematological parameters as presented in reviewed articles on *D. labrax* (mean ± SD or SE*, NA = not available)

BW(gr)	RBC (x10^6 /µL)	WBC (x10^3 /µL)	Hb (g/dL)	Hct (%)	MCV (µm^3)	MCH (pg)	MCHC (g/dL)	TC (x10^3/µL)	Parameters/Authors
3.71 ± 0.32	2.75 ± 0.32	28.5 ± 1.11	10.02 ± 0.41	33.1 ± 1.11	120.36 ± 3.54	36.44 ± 0.99	30.27 ± 1.58	NA	Saleh et al., 2015
15.51 ± 0.21	1.36 ± 0.02	21.03 ± 0.14	7.65 ± 0.05	18.59 ± 0.07	NA	NA	NA	NA	Goda et al., 2020
19.63 ± 0.80	3.72 ± 0.10	11.52 ± 0.13	9.86 ± 0.76	39.87	NA	NA	NA	NA	Abdelmalek et al., 2015 8w
22	3.69 ± 0.18	31.33 ± 6.28	12.77 ± 0.25	31.67 ± 3.79	85.83 ± 5.20	34.62 ± 0.50	40.33 ± 2.17	NA	Saleh et al., 2020
25.70 ± 2.05	4.5 ± 0.12	NA	10.02 ± 0.05	55.1 ± 0.20	122.44 ± 4.10	22.27 ± 0.09	18.18 ± 0.21	NA	Yilmaz et al., 2012*
34.17± 0.06	3.89 ± 0.11	13.23 ± 0.72	13.38 ± 0.15	40.3 ± 2.53	NA	NA	NA	NA	Abdelmalek et al., 2015 12w
50	3.5 ± 0.22	70.20 ± 3.54	9.80 ± 0.54	41.4 ± 1.20	118.00 ± 2.70	28.00 ± 1.00	23.67 ± 0.90	54.00 ± 0.54	Marino et al., 2016*
70.06 ± 0.89	4.63 ± 0.07	28.07 ± 2.28	12.67 ± 2.09	45 ± 2.58	96.63 ± 3.05	27.13 ± 0.70	28.13 ± 0.18	NA	Saleh N.E, 2020*
114 ± 5.9	NA	NA	NA	38.05 ± 1.40	NA	NA	NA	NA	Pavlidis et al., 2007
120-200	NA	NA	4.81 ± 1.45	30.48 ± 4.43	NA	NA	NA	NA	Roque et al., 2010
125	NA	NA	7.2 ± 0.3	32.9 ± 0.9	NA	NA	NA	NA	Roche & Boge, 1996
130-150	NA	NA	NA	30.78 ± 4.41	NA	NA	NA	NA	Yildiz & Altunay, 2011
137.86 ± 30.33	3.51 ± 0.34	30.90 ± 8.35	9.48 ± 0.83	51.18 ± 5	146.20 ± 11.71	27.06 ± 0.98	18.6 ± 1.25	86.08 ± 16.17	Filiciotto et al., 2012
141.97 ± 12.59	4.01 ± 0.60	NA	10.60 ± 1.10	48.38 ± 4.81	122.20 ± 14.66	26.62 ± 3.62	21.96 ± 1.53	NA	Fazio et al., 2018
142.52 ± 11.05	3.02 ± 0.66	NA	6.67 ± 0.87	32 ± 3.48	109.40 ± 18.43	23.28 ± 6.60	21.07 ± 3.41	NA	Fazio et al., 2018
150.9 ± 35.18	3.49 ± 0.28	27.22 ± 5.65	8.90 ± 0.76	49.29 ± 6.17	141.00 ± 11.05	25.50 ± 1.24	18.16 ± 1.33	80.72 ± 19.64	Fazio et al., 2013
155.6 ± 10.3	3.45 ± 0.51	12.97 ± 1.64	11.62 ± 2.77	32.66 ± 4.56	94.6	36.45	38.53	NA	Vectesi et al., 2012*
160	NA	NA	8.83 ± 1.26	NA	NA	NA	NA	NA	Cotou et al., 2012
169 ± 2.2	NA	NA	NA	36 ± 1	NA	NA	NA	NA	Garcia et al., 1992
189.4 ± 80	NA	NA	NA	21.71 ± 2.2	NA	NA	NA	NA	Buscaino et al., 2010
202 ± 42	NA	NA	10.2	30.7 ± 1.8	NA	NA	NA	NA	Petochi et al., 2011
221.7 ± 5.0	2.92 ± 0.18	52.1 ± 4.1	7.49 ± 0.39	31.17 ± 1.57	106.93 ± 5.80	25.72 ± 1.74	24.12 ± 1.74	27.6 ± 2.2	Machado et al., 2019
221.7 ± 5.0	2.96 ± 0.31	48.8 ± 11.0	7.36 ± 0.60	28.33 ± 1.69	96.33 ± 7.32	25.09 ± 3.06	25.97 ± 1.30	25.8 ± 5.7	Machado et al., 2019
412.11 ± 41.55	NA	NA	NA	41.3 ± 4.5	NA	NA	NA	NA	Caruso et al., 2011
688.33 ± 65.37	1.43 ± 0.07	NA	4.60 ± 0.32	24 ± 0.02	NA	NA	NA	NA	Peruzzi et al., 2006
1005.63 ± 93.10	2.17 ± 0.10	NA	5.28 ± 0.3	26 ± 0.02	NA	NA	NA	NA	Peruzzi et al., 2005
1-4 y old	3.16 ± 0.85	19.25 ± 12.55	7.95 ± 1.01	42.15 ± 6.80	NA	NA	NA	43.3 ± 21.10	Alvarez-Pellitero & Pinto, 1987

Table 2. Environmental and external factors as presented in articles of *D. labrax.* (NA= not available)

BW(gr)	T (°C)	pH	Salinity (g/L)	Dis. O_2 (mg/L)	Light (h)	FM/FO %	Anesthetic	Anticoagulant	Manual/Automated analysis	Hb determination method	Daily rate %	Biomass	Parameters/Authors
3.71 ± 0.32	24.0 ± 1.0	8.0 ± 0.2	NA	7.6 ± 1.0	NA	NA	NA	Heparin	A (ERMA-Inc) India	A	NA	NA	Saleh et al., 2015
15.51 ± 0.21	18 ± 1	7.0 ± 0.5	37	NA	12:12	NA	MS 222	Heparin	M	Kit, Diamond, Egypt	5%	NA	Goda et al., 2020
19.63 ± 0.80	19.5-22.6	NA	NA	7.9 ± 0.2	12:12	NA	NA	NA	M	Drabkin & Austin, 1935	manual	2.7	Abdelmalek et al., 2015 8w
22	NA	NA	32	6.0-7.0	NA	NA	Clove oil	heparin	A (AGD Biomedicals)	A	manual	50/tank	Saleh et al., 2020
25.70 ± 2.05	23 ± 1	8.5 ± 0.1	28.2 ± 0.2	7.4 ± 0.1	NA	NA	Clove oil	EDTA	M	Blaxhall and Daisley, 1973	manual	10/tank	Yilmaz & Ergun, 2012
34.17± 0.06	19.5-22.6	NA	NA	7.9 ± 0.2	12:12	NA	NA	NA	M	Drabkin & Austin, 1935	satiation	2.7 kg/m3 (67 fish/tank	Abdelmalek et al., 2015 12w
50	20-22	8	30	NA	12	NA	NA	EDTA	A (SEAC, Italy)	A	auto	NA	Marino et al., 2016
70.06 ± 0.89	24.4 ± 1.2	7.2 ± 0.21	38	7	11:13	NA	NA	Heparin	A (ERMA-Inc.) India	A	satiety	25/tank	Saleh N.E., 2020
114 ± 5.9	18.4-18.6	7.74-8.04	36-40	4.5-5.3	NA	NA	2PE	EDTA	M	M	ad libidum	5-7kg/m^3	Pavlidis et al., 2007
120-200	26.5-27.5	NA	33	6.5-7.5	NA	NA	NA	Heparin	M	Kit, Linear Chemicals, Spain	NA	300/tank	Roque et al., 2010
125	15 ± 1	NA	NA	NA	NA	NA	NA	Heparin	M	Drabkin & Austin, 1935	NA	NA	Roche & Boge, 1996
130-150	18 ± 3	7.5	NA	12	NA	NA	NA	Heparin	M	M	NA	NA	Yildiz &Altunay, 2011
137.86 ± 30.33	21.47	7.03	38	7.51	NA	NA	2PE	EDTA	A (SEAC, Italy) & M	Kit, Roach GmbH, Germany	NA	37.5 kg/m^3	Filiciotto et al., 2012
141.97 ± 12.59	13.40 ± 0.18	NA	NA	5.6 ± 0.07	12:12	45/20	2PE	EDTA	A (SEAC, Italy)	A	NA	31 kg/m^3	Fazio et al., 2018
142.52 ± 11.05	23.20 ± 0.22	NA	NA	3.8 ± 0.05	13:11	45/20	2PE	EDTA	A (SEAC, Italy)	A	NA	31 kg/m^3	Fazio et al., 2018
150.9 ± 35.18	NA	NA	NA	NA	NA	NA	NA	EDTA	A (SEAC, Italy)	A	NA	NA	Fazio et al., 2013
155.60 ± 10.3	23.7-24.5	8.01	38	7.02	14	NA	NA	Heparin	M	Drabkin & Austin, 1935	manual	NA	Vectesi et al.,., 2012
160	22-25	NA	38	7	12:12	NA	Ice	Heparin	M	Drabkin & Austin, 1935	NA	12/tank	Cotou et al., 2012
169 ± 2.2	16.5 ± 1	NA	36	NA	NA	NA	NA	Heparin	M	NA	NA	NA	Garcia et al., 1992
189.4 ± 80	NA	NA	NA	NA	NA	NA	2PE	NA	M	NA	NA	5kg/m^3	Buscaino et al., 2010
202 ± 42	20.2 ±1.5	7.7 ± 0.24	NA	9.8 ± 1.1	NA	NA	MS 222	NA	A (sensor cassettes (Roche Diagnostics)	A, Roche Diagnostics	0.5%	11kg/m^3	Petochi et al., 2011
221.7 ± 5.0	25.4 ± 0.5	NA	35 ± 1	NA	12:12	62.4/18.4	NA	Heparin	M	M, Spinreact kit, Spain	NA	NA	Machado et al., 2019
221.7 ± 5.0	25.4 ± 0.5	NA	35 ± 1	NA	12:12	62.4/18.2	NA	NA	M	>>	NA	NA	Machado et al., 2019
412.11 ± 41.55	20	8.2	38	NA	NA	45/22	MS 222	Heparin	M	NA	satiation	10/tank	Caruso et al., 2011
1005.63 ± 93.10	NA	NA	NA	NA	NA	NA	NA	EDTA	M	M, Spinreact kit, Spain	manual	NA	Peruzzi et al., 2005 T
688.33 ± 65.37	NA	NA	NA	NA	NA	NA	NA	EDTA	M	>>	manual	NA	Peruzzi et al., 2005 D
1-4 y old	NA	NA	37.8	NA	NA	NA	MS 222	NA	M	M, hemocue photometer	NA	NA	Alvarez-Pellitero & Pinto 1987

Table 3. Hematological parameters as presented in reviewed articles on *S. aurata* (mean ± SD or SE*, NA = not available)

BW (gr)	RBC ($x10^6$/µL)	WBC ($x10^3$ /µL)	Hb (g/dL)	Hct (%)	MCV ($µm^3$)	MCH (pg)	MCHC (g/dL)	TC ($x10^3$ /µL)	Parameters/Authors
32 ± 0.01	2.68 ± 0.28	60.1 ± 6.3	7.19 ± 0.65	29.1 ± 2.0	109.4 ± 10.5	27.0 ± 2.6	24.7 ± 1.3	NA	Guerreiro, 2016
50	3.77 ± 0.13	74.70 ± 2.15	11.75 ± 0.29	43.62 ± 1.37	116.10 ± 2.65	31.29 ± 0.48	27.07 ± 0.48	36.70 ± 0.56	Marino et al., 2016*
60.65 ± 12.74	NA	NA	12.43 ± 2.11	NA	NA	NA	NA	NA	Henry et al., 2015
82.64 ± 12.06	2.82 ± 0.54	NA	9.32 ± 1.98	37.21 ± 6.35	135.5 ± 22.02	33.10 ± 3.75	24.75 ± 2.40	NA	Montero et al., 2001
85.5 ± 1.58	2.66 ± 0.07	NA	7.16 ± 0.47	32.8 ± 1.68	NA	NA	NA	NA	Ballester-Lozano, 2015
89.81 ± 1.14	3.01 ± 0.04	36.46 ± 1.20	11.86 ± 0.15	61.33 ± 2.01	204.17 ± 6.76	39.63 ± 0.23	19.33 ± 0.54	12.66 ± 1.45	Gelibolu et al., 2018*
90.1 ± 19.6	2.23 ± 0.11	NA	4.55 ± 0.42	21.34 ± 1.42	132.2 ± 13.9	32.59 ± 3.04	23.49 ± 1.54	NA	Tort et al., 2002
96.7 ± 2.53	NA	NA	8.90 ± 0.44	NA	NA	NA	NA	NA	Perez-Sanchez 2015
100 ± 25	2.3 ± 0.5	36.4 ± 6.1	3.4 ± 0.6	32.3 ± 4.2	NA	13.2 ± 1.4	11.8 ± 1.5	NA	Rigos et al., 2013*
123.1 ± 4.2	NA	NA	NA	20.2 ± 0.2	NA	NA	NA	NA	Goncalves et al., 2020
144.62 ± 13.49	3.48 ± 0.51	NA	9.62 ± 0.74	42.52 ± 5.12	124.5 ± 20.22	28.26 ± 4.77	22.91 ± 3.22	NA	Fazio et al., 2018
150-190	NA	NA	4.16 ± 0.6	25.8 ± 2.5	NA	NA	NA	NA	Molinero & Gonzalez, 1995
162 ± 45	NA	NA	NA	38.5 ± 5.8	NA	NA	NA	NA	Palstra et al., 2020
172.6 ± 23.7	NA	NA	NA	18.57 ± 2.3	NA	NA	NA	NA	Buscaino et al., 2010
182.30 ± 29.75	2.74 ± 0.13	45.73 ± 2.82	9.07 ± 0.44	49.83 ± 2.51	181.60 ± 1.99	33.05 ± 0.74	18.34 ± 0.61	104.75 ± 36.73	Fazio et al., 2015
190-230	NA	NA	NA	29.23 ± 3.95	NA	NA	NA	NA	Yildiz & Altunay, 2011
203 ± 5.7	2.8 ± 0.13	NA	7.49 ± 0.42	32.1 ± 1.1	115.4 ± 4.2	26.1 ± 2.5	23.4 ± 2.0	NA	Pages et al., 1995
218.97 ± 3.94	NA	NA	11.63 ± 0.03	50.1 ± 1.21	122.8 ± 1.44	NA	22.1 ± 0.36	NA	Mente et al., 2012
277.8 ± 38	2.7 ± 0.7	19.5 ± 5.0	NA	NA	NA	NA	NA	NA	Zupan et al., 2015
315.3 ± 7.2	NA	NA	NA	40.57 ± 1. 56	NA	NA	NA	NA	Pavlidis et al., 2007
353.18 ± 57.3	3.50 ± 0.08	68.08 ± 2.95	8.00 ± 0.23	50.35 ± 1.18	144.40 ±	23.42 ± 0.82	16.28 ± 0.58	60.91 ± 1.94	Fazio et al., 2012*
359.3 ± 26.4	3.5 ± 0.5	86 ± 5	11.0 ± 2.5	45.6 ± 6.7	128.0 ± 9.4	30.5 ± 3.7	24.1 ± 3.9	47.6 ± 24.4	Gultepe et al., 2012

Table 4. Environmental and external factors as presented in articles of *S. aurata*. (NA= not available)

BW(gr)	T (°C)	pH	Salinity (g/L)	Dis. O_2 (mg/L)	Light (h)	FM/FO %	Anesthesia	Anticoagulant	Manual/Automated analysis	Hb determination method	Daily rate %	Biomass	Parameters/Authors
32 ± 0.01	18+/-0.5	NA	35+/-1	7	NA	31.4/13.7	NA	Heparin	M	M Spinreact kit, Spain	satiation	22 fish/tank	Guerreiro, 2016
50	20-22	8	30	NA	12:12	NA	MS 222	EDTA	A (SEAC, Italy)	A	NA	NA	Marino et al., 2016
60.65 ± 12.74	20-27	NA	32	NA	Natural	NA	Clove oil	Heparin	M	Drabkin	2-2.5%	NA	Henry et al., 2015
82.64 ± 12.06	19-22.5	NA	NA	6.2 - 10.5	12:12	NA	none	Heparin	A (System 800) & M	A	2.50%	12kg/m^3	Montero et al., 2001
85.5 ± 1.58	24	NA	NA	NA	Natural	0/13.9	MS-222	Heparin	M	HemoCue B-Haemoglobin Analyser	satiation	NA	Ballester-Lozano, 2015
89.81 ± 1.14	24.77±0.18	7.68±0.04	37.35 ± 0.1	11 ± 0.16	NA	45.39/20.34	2PE	EDTA	A (Hospital)	A (Hospital)	NA	50/tank	Gelibolu et al., 2018
90.1 ± 19.6	15+/-0.5	NA	38	NA	12:12	NA	none/clove oil/2PE	NA	M	M Boehringer-Mannheim kit	1%	6kg/m^3	Tort et al., 2002
96.7 ± 2.53	19-25	NA	seawater	NA	NA	68/9	MS 222	Heparin	M	HemoCue B-Haemoglobin Analyser	NA	NA	Perez-Sanchez et al., 2015
100 ± 25	20	NA	38	NA	NA	20.55/15.72	Clove oil	Heparin	M	Detect X® Hemoglobin kit, UK	1%	7kg/m^3	Rigos et al., 2013
123.1 ± 4.2	23.3 ± 1.5	NA	33–35	5.5	Natural	47.2/18.4	AQUI-S	Heparin	M	NA	satiation	NA	Goncalves et al., 2020
144.62 ± 13.49	23.2+/-0.22	NA	NA	3.8+/-0.05	13:11	NA	2PE	EDTA	A (SEAC, Italy)	A	NA	36kg/m^3	Fazio et al., 2018 W
150-190	15-16	7.4-7.7	36-38	saturation	NA	NA	NA	NONE	M	Blaxhall and Daisley, 1973	1%	NA	Molinero & Gonzalez, 1995
162 ± 45	18 ± 0.5	7.1–7.8	35	6.0 ± 0.5	NA	NA	MS 222	NA	NA	NA	NA	7kg/m^3	Palstra et al., 2020
172.6 ± 23.7	NA	NA	NA	NA	Natural	NA	2PE	NA	M	NA	NA	NA	Buscaino et al., 2010
182.30 ± 29.75	21	NA	38	5	NA	NA	none	EDTA	A (SEAC, Italy)	A	NA	<5kg/m^3	Fazio et al., 2015
190-230	18 ± 3	7.5	NA	12	NA	NA	2PE	Heparin	M	M	NA	10/tank	Yildiz & Altunay, 2011
203 ± 5.7	15 ± 0.5	NA	42	NA	12:12	NA	NA	Heparin	M	Drabkin & Austin, 1935	NA	15kg/m^3	Pages et al., 1995
218.97 ± 3.94	10.5-26.7	8-8.1	NA	8.1-9.6	NA	46/17	NA	NA	NA	NA	NA	15 kg/m^3	Mente et al., 2012
277.8 ± 38	12.1-19.1	NA	38	NA	NA	NA	2PE	Heparin	M	NA	NA	NA	Zupan et al., 2015
315.3 ± 7.2	18.4-18.6	7.74-8.04	36-40	4.5-5.3	NA	NA	2PE	EDTA	M	NA	satiation	NA	Pavlidis et al., 2007
353.18 ± 57.3	19.47	8.22	36.37ppt	8.4	Natural	NA	2PE	EDTA	A (SEAC, Italy) & M	A & M (Roach GmbH, Germany)	NA	5-7kg/m^3	Fazio et al., 2012
359.3 ± 26.4	19.6-24.7	7.5	36 ± 0.5	8 ± 0.5	NA	NA	MS 222	Heparin	M	van Kampen and Zijlstra, 1961	NA	20kg/m^3	Gultepe et al., 2012

Table 5. Recommendation for standardization of reporting units used in blood count.

Component	Conventional	SI	Conversion factor Conventional to SI unit
Erythrocytes (RBC)	$10^6/\mu L$	$10^{12}/L$	1
Haematocrit (Hct)	%	Volume fraction	0.01
Haemoglobin (Hb)	g/dL	g/L	10
	g/dL	mmol/L (Fe)	0.621
Leucocytes (WBC) differential count	$10^3/\mu L$	$10^9/L$	1
Leucocrit	%	Volume fraction	0.01
Mean corpuscular haemoglobin (MCH)	µg	pg	10^6
	pg	fmol (Fe)	0.621
Mean corpuscular haemoglobin concentration (MCHC)	g/dL	g/L	10
	g/dL	mmol/L (Fe)	0.621
Mean corpuscular volume (MCV)	μm^3	fL	1
Thrombocytes (TC)	$10^3/\mu L$	$10^9/L$	1

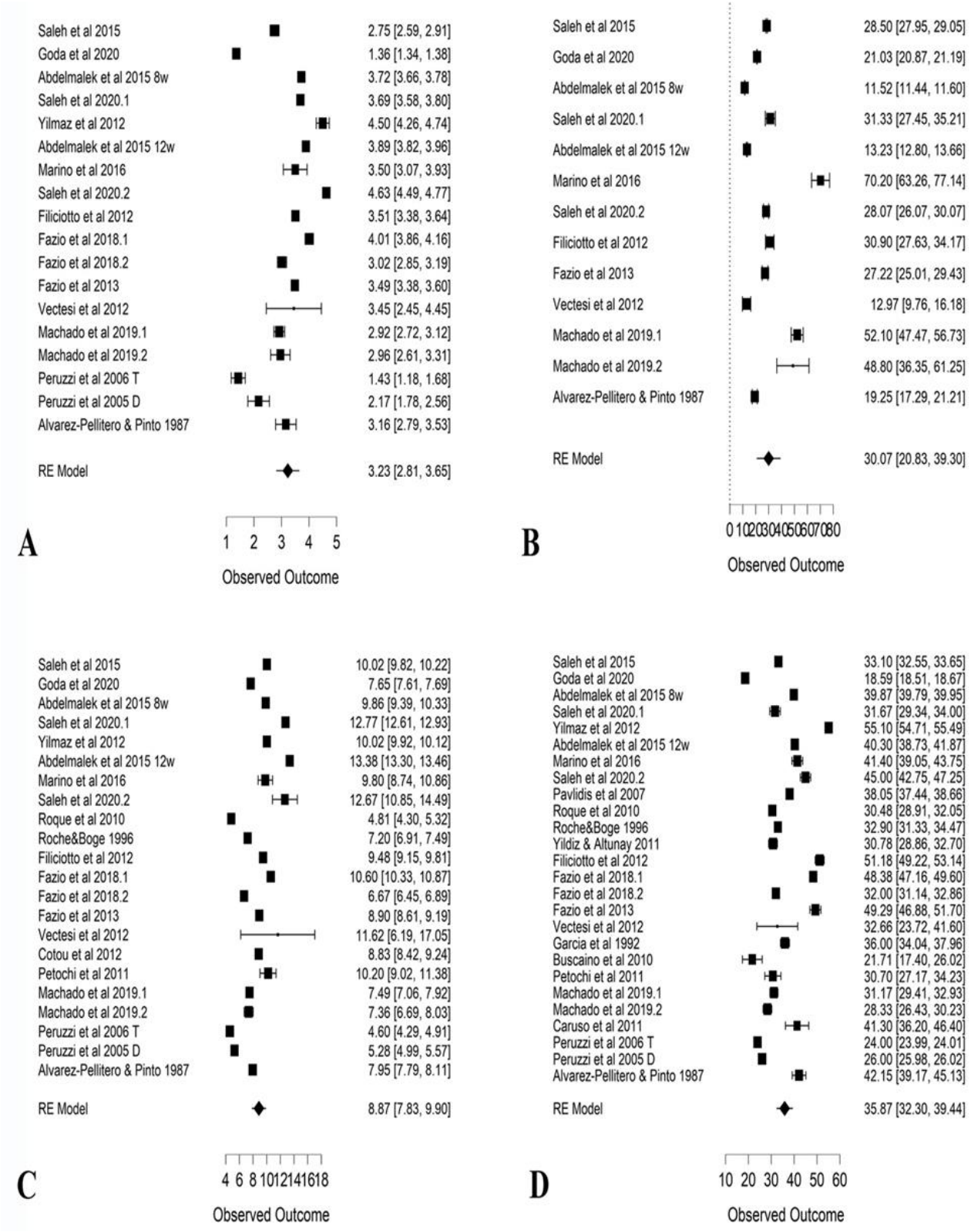

Figure. 2. *D. labrax* blood parameters forest plots with mean and 95% confidence intervals A. RBC, B. WBC, C. Hb, D. Hct.

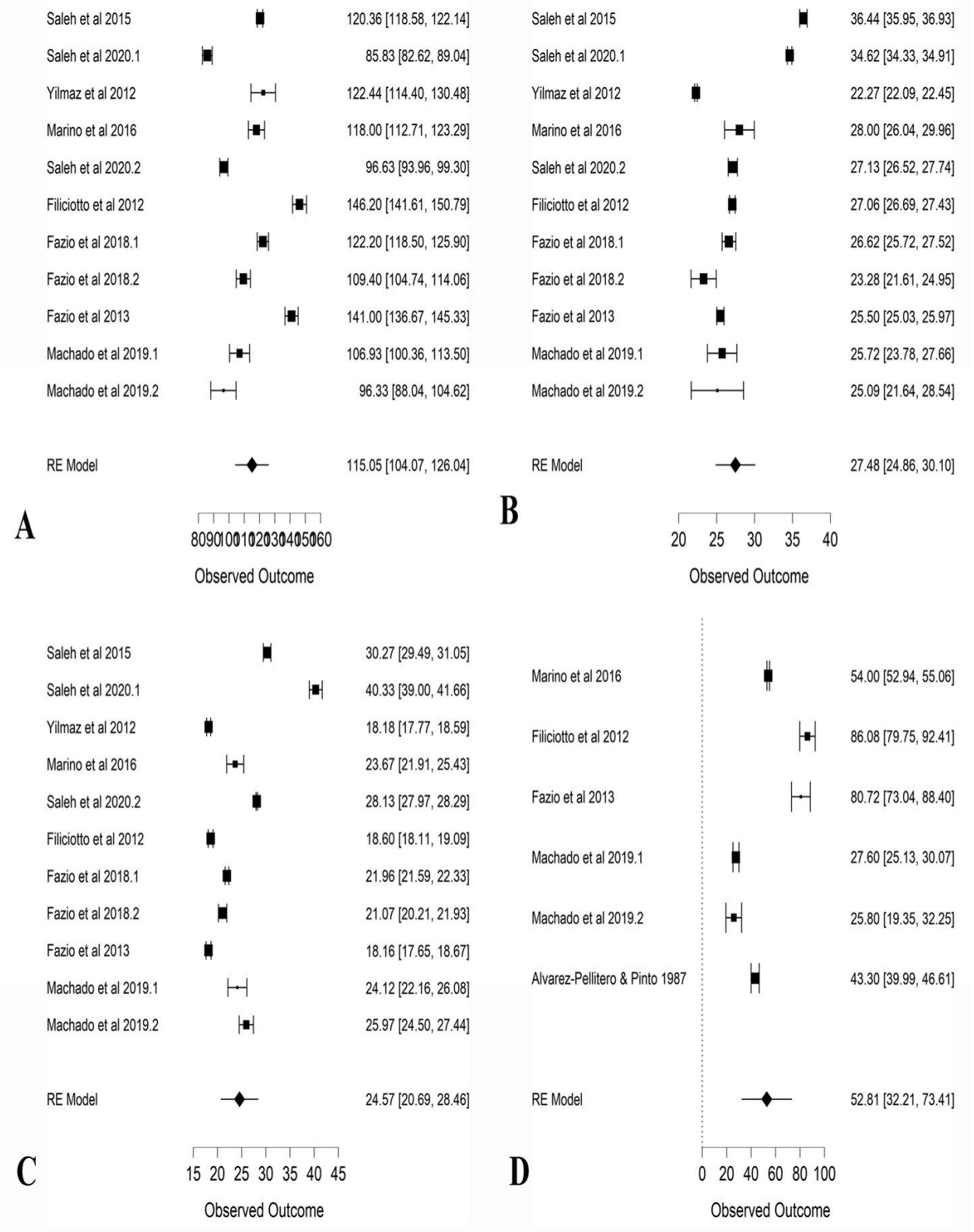

Figure. 3. *D. labrax* blood parameters forest plots with mean and 95% confidence intervals A. MCV, B. MCH, C. MCHC, D. TC.

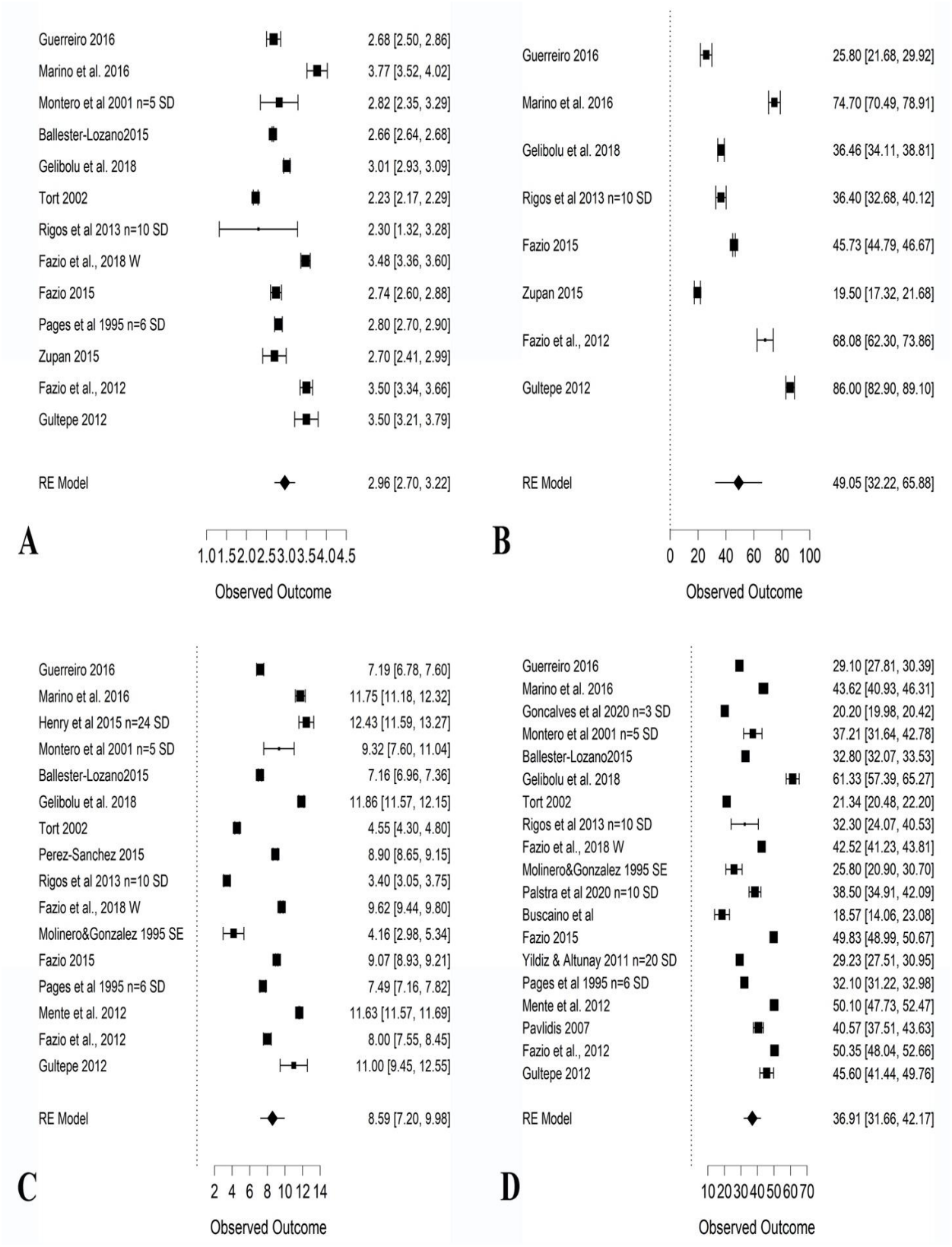

Figure. 4. *S. aurata* blood parameters forest plots with mean and 95% confidence intervals A. RBC, B. WBC, C. Hb, D. Hct.

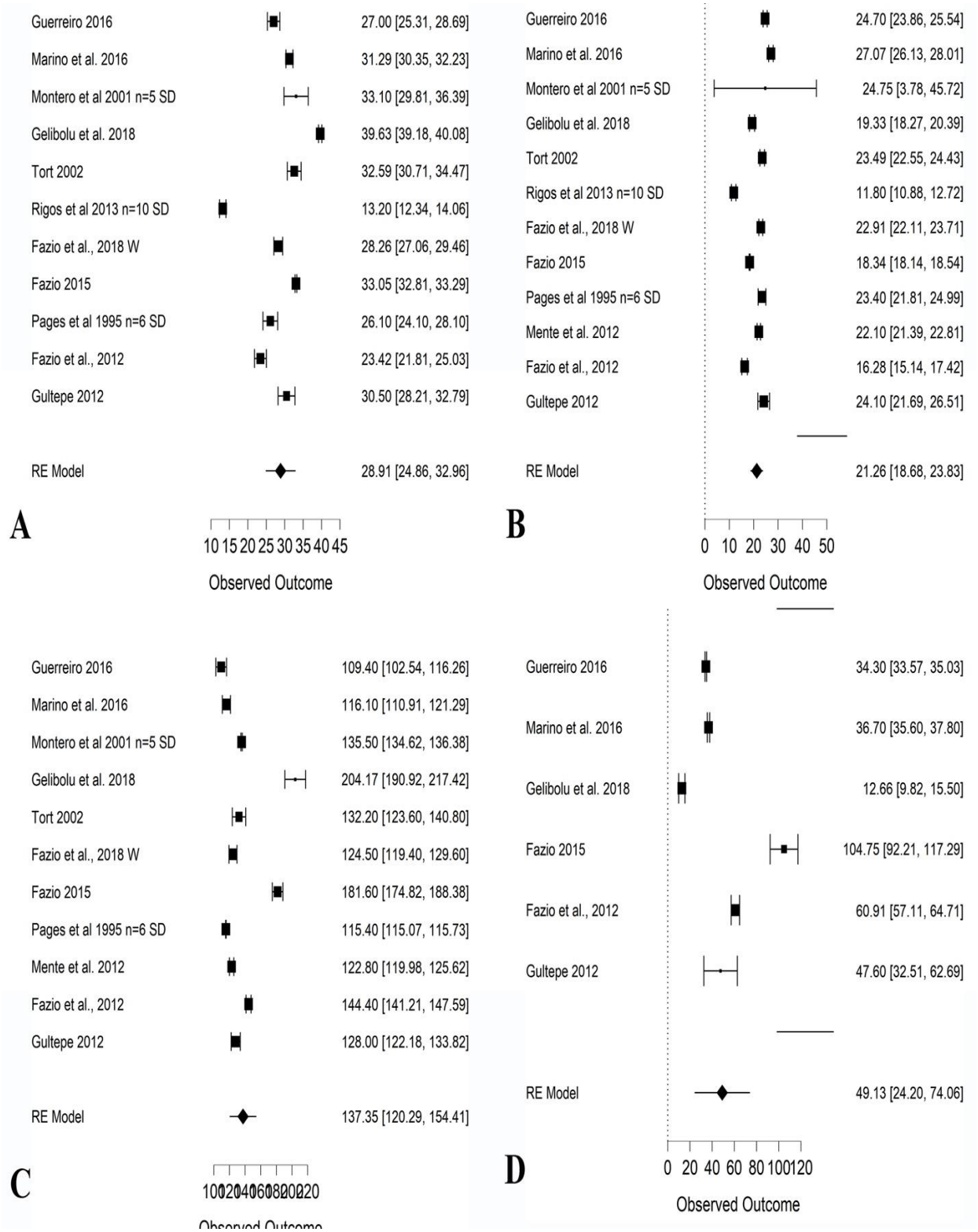

Figure. 5. *S. aurata* blood parameters forest plots with mean and 95% confidence intervals A. MCV, B. MCH, C. MCHC, D. TC.